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[1] J. B. Austin and R. H. H. Pierce, *J. Amer. Chem. Soc.* **55**, 661 (1933).

[2] J. R. Goldsmith, D. L. Graft and O. I. Joensuu, *Geochim. et Cosmochim. Acta* **7**, 221 (1955).

[3] S. T. Yoffe and A. N. Nesmeyanov, *Handbook of Magnesium-Organic Compounds* Vol. II, p. 239. Pergamon Press, London (1956).

Abbreviations are used freely in *Tetrahedron*, particularly in setting the experimental section. For the most part these are not followed by a full stop (period). Among the more commonly used abbreviations, these may be listed:

g kg mm cm ml cc cm^3 sec min hr n_D^{25} $[\alpha]_D^{25}$ 25° (without C which is always understood) but m.p., b.p., l. (liter). in. (inch) but in^2.

New compounds should be indicated by underlining the name (for italics) at its first mention (including headings) in the experimental section only, and by giving analytical results in the form: (Found: C, 62·9; H, 5·4. $C_{12}H_{12}O_4N$ requires C, 63·2; H 5·3%).

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STUDIES IN THE XANTHONE SERIES—III*

PREPARATION AND REACTIONS OF 1-ACETYL-2-HYDROXYXANTHONE

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Abstract—The orientation and reactions of 1-acetyl-2-hydroxyxanthone (I; R_1 = Ac, $R_2 = R_3$ = H) leading to the synthesis of angular furanoxanthones (III; R = Me) and (IV) and pyronoxanthones of the type (V) are described. The ultra-violet spectra of these extended xanthone systems are discussed.

REACTIONS of 1-acetyl-2-hydroxyxanthone (I; R_1 = Ac, $R_2 = R_3$ = H) were studied in an attempt to prepare physiologically active molecules of simple chemical structure, analogous to biologically active chromones such as khellin.[1] The ketone itself could not be obtained from 2-hydroxyxanthone (I; $R_1 = R_2 = R_3$ = H) (or from its acetyl or methyl derivative) which, unlike the 1-hydroxy-isomer,[2] did not undergo acetylation under Fries or Friedel–Crafts conditions. In another unsuccessful attempt at preparing the ketone, the diphenyl ether (II; $R_1 = R_2$ = H, R_3 = OMe) (obtained from *o*-chlorobenzoic acid and *p*-methoxyphenol)[10] was treated with a mixture of aluminium chloride and acetyl chloride, but gave only 2-methoxyxanthone (I; R_2 = Me, $R_1 = R_3$ = H). When, in order to prevent this premature cyclisation, the ethyl ester (II; R_1 = Et, R_2 = H, R_3 = OMe) was used, the following products were obtained: Two diphenyl ethers (II; R_1 = Et, R_2 = Ac, R_3 = OH and R_1 = H, R_2 = Ac, R_3 = OH), a diacetyldiphenyl ether of unknown constitution, and the required ketone (I; R_1 = Ac, $R_2 = R_3$ = H), but in small yield only. The incidental formation of the ketone under Friedel–Crafts conditions prompted cyclisation of the acetyl compound (II; R_1 = H, R_2 = Ac, R_3 = OH) with aluminium chloride-acetyl chloride which gave the ketone in 37% yield. *Poly*phosphoric acid, could also be used as a cyclising agent when the reaction temperature was kept within the range of 60–80°. No reaction occurred below 60°, while above 80° phosphono-2-oxyxanthone (I; $R_1 = R_3$ = H, R_2 = P(O)(OH)$_2$) together with some 2-hydroxyxanthone (I; $R_1 = R_2 = R_3$ = H) were the main products. The latter two products were also formed when 1-acetyl-2-hydroxyxanthone was heated with *poly*phosphoric acid above 80°, thus demonstrating the lability of the 1-acetyl-group. By contrast, the 2-acetyl and the 4-acetyl-1-hydroxyxanthone proved to be stable to hot *poly*phosphoric acid.[3] De-acylation in sterically hindered aromatic ketones by *poly*phosphoric acids[4] and other acids[5] has been reported previously.

* Part II was published in *J. Chem. Soc.* 1790 (1958).

[1] C. P. Huttrer and E. Dale, *Chem. Rev.* **48**, 543 (1951).
[2] J. S. H. Davies, F. Scheinmann and H. Suschitzky, *J. Chem. Soc.* 2140 (1956).
[3] F. Scheinmann and H. Suschitzky, Unpublished results.
[4] H. R. Snyder and R. W. Roeske, *J. Amer. Chem. Soc.* **74**, 5820 (1952).
[5] W. M. Schubert and H. K. Latourette, *J. Amer. Chem. Soc.* **74**, 1829 (1952).

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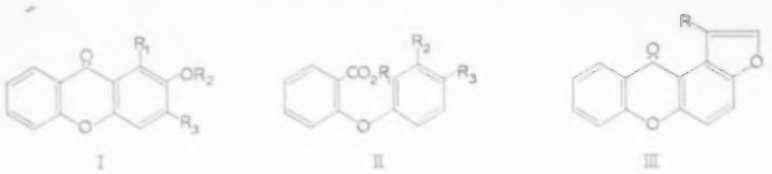


I II III

Since cyclisation of the diphenyl ether (II; $R_1 = H$, $R_2 = Ac$, $R_3 = OH$) may occur in two directions yielding two isomers (I; $R_1 = Ac$, $R_2 = R_3 = H$ or $R_1 = R_2 = H$, $R_3 = Ac$), the resulting ketone had to be orientated. It was not possible to show the presence of a 1:4-diketone structure by means of hydrazine or *o*-phenylenediamine. In an unsuccessful attempt to prepare the 1-acetyl-isomer (I; $R_1 = Ac$, $R_2 = R_3 = H$) unambiguously, 1-formyl-2-hydroxyxanthone (I; $R_1 = CHO$, $R_2 = R_3 = H$) was made to react with diazomethane yielding the oxide (I; $R_1 = CH—CH_2$ with O, $R_2 = R_3 = H$) which, on treatment with 2-N-sulphuric acid gave the furanoxanthone (III; $R = H$). The reaction of diazomethane with *o*-hydroxy-aldehydes as a preparative route to furanocompounds is being investigated by us. Formation of furanostructures by hydrolysis of ethylene oxides in the case of a benzene and also a phenanthrene ethylene oxide[6,7] has been observed previously. In another unsuccessful synthesis of the 1-acetyl compound the acid chloride (I; $R_1 = COCl$, $R_2 = Ac$, $R_3 = H$), obtained by permanganate oxidation of the aldehyde (I; $R_1 = CHO$, $R_2 = Ac$, $R_3 = H$) followed by treatment with thionyl chloride, could not be made to react with dimethyl cadmium or with diazomethane.

Structural assignment of the ketone was next attempted by oxidation experiments but none of the standard methods applicable to ketones was of any avail. A modified hypobromite oxidation described recently for sterically hindered ketones[8] afforded a 1-tribromo-acetyl-2-methoxyxanthone (I; $R_1 = CO{\cdot}CBr_3$, $R_2 = Me$, $R_3 = H$). Formation of an *ω*-halo acetophenone type of compound actually supports placing the acetylgroup in the 1-position, since only methyl arylketones with two *ortho*-substituents are known to form stable trihalo-acetyl-derivatives in haloform reactions.[9] Attempts to hydrolyse the tribromocompound proved abortive. When, however, a cold solution of the methoxyketone (I; $R_1 = Ac$, $R_2 = Me$, $R_3 = H$) in concentrated sulphuric acid was treated with chromium trioxide 2-methoxy-xanthone-1 carboxylic acid (I; $R_1 = CO_2H$, $R_2 = Me$, $R_3 = H$) identical with the oxidation-product of 1-formyl-2-methoxyxanthone (I; $R_1 = CHO$, $R_2 = Me$, $R_3 = H$) was obtained. Additional constitutional evidence for the structure of the hydroxy ketone also follows from its lack of reactivity towards ketonic reagents, the absence of chelation (negative ferric reaction), the ease of de-acylation (cf. above) and finally from the similarity between the ultra-violet spectrum of its methyl ether and that of 1-formyl-2-methoxyxanthone (Fig. 1).

The hydroxyketone proved a useful starting material for the preparation of angular furano- and pyrono-xanthones. It condensed readily with ethyl bromoacetate to give the xanthyloxyacetate (I; $R_1 = Ac$, $R_2 = CH_2{\cdot}CO_2Et$, $R_3 = H$) and by

[6] J. W. Cook and W. H. S. Thomson, *J. Chem. Soc.* 395 (1945).
[7] V. I. Pansevich-Kolyada and Z. B. Idel'chik, *Zh. obshch. khim.* **25**, 2215 (1955).
[8] J. D. Edwards, Jr. and J. L. Cashaw, *J. Amer. Chem. Soc.* **78**, 3821 (1956).
[9] R. C. Fuson and B. A. Bull, *Chem. Rev.* **15**, 275 (1934).

hydrolysis of the latter the corresponding acid (I; $R_1 = Ac$, $R_2 = CH_2{\cdot}CO_2H$, $R_3 = H$). Cyclisation and decarboxylation occurred when the latter compound was heated with a mixture of sodium acetate and acetic anhydride yielding 4′-methylfurano(3′:2′–1:2)xanthone (III; R = Me). Its ultra-violet absorption spectrum (Fig. 2) resembles that of the angular furano(3′:2′–1:2)xanthone (III; R = H) prepared unambiguously[10] from 1-formyl-2-hydroxyxanthone. This incidentally

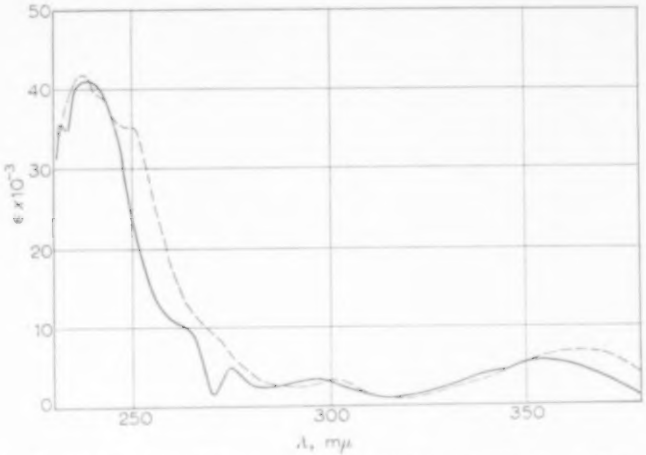


FIG. 1. Ultra-violet absorption spectra of 1-acetyl-2-methoxyxanthone (– – –) and of 1-formyl-2-methoxyxanthone (———) in methanol.

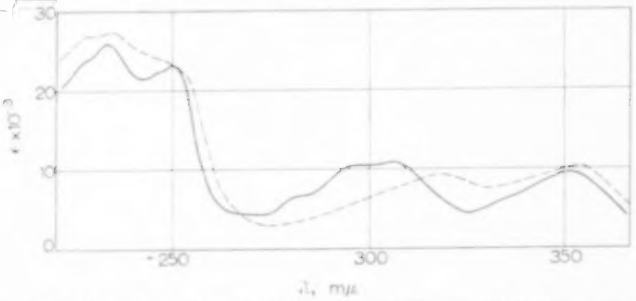


FIG. 2. Ultra-violet absorption spectra of 4′-methylfurano (3′:2′–1:2) xanthone (– – –) and of furano(3′:2′–1:2)xanthone (———) in methanol.

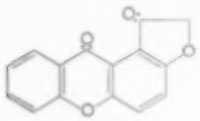
affords additional confirmation for the constitution of the hydroxyketone (I; $R_1 = Ac$, $R_2 = R_3 = H$).

Bromination of the ketone in acetic acid gave the ω-bromocompound (I; $R_1 = CO{\cdot}CH_2Br$, $R_2 = R_3 = H$) which was readily cyclised with sodium acetate in boiling aqueous ethanol to 4′:5′-dihydro-4′-oxofurano(3′:2′–1:2)xanthone (IV).

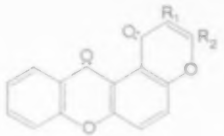
Two methods for making angular γ-pyronoxanthones from the ketone were examined. In the first the impure ester (I; $R_1 = CO{\cdot}CH_2{\cdot}CO{\cdot}CO_2Et$, $R_2 = R_3 = H$) obtained by a Claisen condensation with diethyl oxalate, was ring-closed in ethanol with hydrochloric acid to the γ-pyronoxanthone (V; $R_1 = H$, $R_2 = CO_2Et$). In

[10] J. S. H. Davis, F. Lamb and H. Suschitzky, *J. Chem. Soc.* 1790 (1958).

the second, the γ-pyronoxanthone (V; R_1 = COPh, R_2 = Ph) was prepared by a Kostanecki–Robinson reaction from the ketone with benzoic anhydride and sodium benzoate.



IV



V

Comparison between the ultra-violet absorption spectrum of xanthone and those of its extended ring-systems possessing a conjugated angular ring in the 1:2-positions reveals an interesting feature: the latter compounds show a marked depression in the intensity of the principal absorption band without appreciable change in the location of the maximal absorption (see Table 1), e.g. xanthone absorbs maximally at 238 mμ, ε = 44,200, while furano(3′:2′–1:2)xanthone (III; R = H) absorbs maximally at 233 mμ, ε = 25,800. A similar spectral behaviour is observed in 1-formyl-2-hydroxyxanthone which, owing to chelation, may be regarded as equivalent to a xanthone with a fused conjugated angular ring. The intensity depression in the oxofuranoxanthone (IV; see Table 1) suggests predominance of the conjugated enol- over the

TABLE 1. MAIN ABSORPTION MAXIMA OF XANTHONE AND RELATED COMPOUNDS IN METHANOL

Compound	λ_{max} (mμ)	ε_{max}
Xanthone	238	44,200
Furano(3′:2′–1:2)xanthone	233	25,800
4′-Methylfurano(3′:2′–1:2)xanthone	235	27,300
4′:5′-Dihydro-4′oxofurano(3′:2′–1:2)xanthone	229	29,500
1-Formyl-2-hydroxyxanthone	241	32,600
1-Formyl-2-methoxyxanthone	239	41,000
1-Acetyl-2-hydroxyxanthone	237	35,700
1-Acetyl-2-methoxyxanthone	238	41,800
6′-Ethoxycarbonyl-4′-pyrono(3′:2′–1:2)xanthone	218	26,000
4′-Pyrono(3′:2′–1:2)xanthone-6′-carboxylic acid, hydrate	221	24,600
6′-Pyrono(3′:2′–1:2)xanthone	245	44,600
5′-Methyl-6′-pyrono(3′:2′–1:2)xanthone	246	42,700

keto-form. In contrast 6′-pyrono(3′:2′–1:2)xanthone and its methyl-homologue[10] which have a non-conjugated angular ring and also 1-formyl- and -acetyl-2-methoxyxanthone in which chelation is prevented, show no significant reduction in the intensity of their chief absorption band relative to that of xanthone. The absence of any marked intensity changes in 1-acetyl-2-hydroxyxanthone is probably due to steric effects which interfere with effective chelation by dislodging the acetyl-group from the plane of the xanthone ring.

Inspection of molecular models (Courtaulds) reveals that the presence of a conjugated angular ring next to the xanthone carbonyl group moderately opposes adoption

of uniplanarity of the xanthone system, thus causing the molecule to assume a non-planar structure. This steric hindrance of resonance is associated with intensity decreases which are more pronounced than the change in the wavelength of maximum absorption (cf. Table 1). The spectroscopic behaviour of 1:2-substituted xanthones appears to be analogous to that of *ortho*-substituted ketones related to acetophenones in which similar changes in their electronic spectra on *ortho*-substitution are interpreted as moderate spatial interference with a uniplanar arrangement of the molecule.[11,12] Benzo- and naphtho-cyclenones have recently been found to show on substitution similar changes in their ultra-violet spectra, which is taken as indicative of steric interference with mesomerism.[13,14]

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EXPERIMENTAL

Ultra-violet absorption spectra were measured in methanol and are quoted as λ_{max} (mμ) with ε in parentheses.

Fries rearrangements of 2-acetoxyxanthone

2-Acetoxyxanthone[15] did not undergo rearrangement in nitrobenzene with aluminium chloride at room temperature nor in the absence of a solvent at 100–110°, nor on treatment in acetic acid with BF_3-ether catalyst at 90° for 2 hr. Starting material and 2-hydroxyxanthone were the only products.

Attempted Friedel–Crafts acetylation

(a) 2-Acetoxy-, 2-hydroxy-, and 2-methoxyxanthone gave only starting material on acetylation under Friedel–Crafts conditions.

(b) To a solution of 2′-carboxy-4-methoxydiphenyl ether[10] (2·44 g) in *sym*-tetrachloroethane (50 ml) was added a suspension of powdered aluminium chloride (3·2 g) in the same solvent (70 ml) containing acetyl chloride (0·94 g). The mixture was stirred for 4·5 hr at room temperature and then allowed to stand for 3 days. Starting material and 2-methoxyxanthone[10] (74%) only were obtained.

2′-Ethoxycarbonyl-4-methoxydiphenyl ether

The parent acid[10] (56·2 g) in ethanol (215 ml) was esterified with dry hydrochloric acid gas for 12 hr. The solvent was driven off, and the residue taken up in chloroform (150 ml) and starting material removed by extraction with sodium hydroxide solution (2 N). Evaporation of the organic layer gave the crude ester (84%) m.p. 39–42°. On distillation (210°/9 mm) the *ester* solidified as white crystals, m.p. 43° (Found: C, 70·2; H, 5·9. $C_{16}H_{16}O_4$ requires C, 70·6; H, 5·9%).

3-Acetyl-4-hydroxy-2′-ethoxycarbonyldiphenyl ether

Powdered aluminium chloride (64 g) carbon disulphide (550 ml), acetyl chloride (14·4 ml) and crude ester (25 g) were refluxed with stirring for 3 hr and then left standing overnight. The residual gum, obtained by driving off the solvent, was treated with hydrochloric acid (30 ml) and crushed ice, and the resulting reaction

[11] E. A. Braude, F. Sondheimer and W. F. Forbes, *Nature, Lond.* **173**, 117 (1954).
[12] G. D. Hedden and W. G. Brown, *J. Amer. Chem. Soc.* **75**, 3744 (1953).
[13] R. Huisgen, I. Ugi, E. Rauenbusch, V. Vossius and H. Oertel, *Ber. Dtsch. Chem. Ges.* **90**, 1946 (1957).
[14] R. Huisgen and U. Rietz, *Ber. Dtsch. Chem. Ges.* **90**, 2768 (1957).
[15] St. von Kostanecki and R. Rutishauser, *Ber. Dtsch. Chem. Ges.* **25**, 1648 (1892).

mixture extracted with chloroform (230 ml), leaving an insoluble substance A (1·42 g). From the chloroform layer an alkaline extract B was produced with 2 N-sodium-hydroxide (3 × 250 ml). Removal of the chloroform and fractional distillation of the residue furnished pure *3-acetyl-2′-ethoxycarbonyl-4-hydroxydiphenyl ether* as a yellow liquid (14·7 g), b.p. 199–200°/2 mm (Found: C, 68·3; H, 5·4. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·4%). It gave a green-brown ethanolic ferric reaction and a red precipitate with Brady's reagent.

1-Acetyl-2-hydroxyxanthone

(a) Acidification of the alkaline extract B (see above) gave a solid which, after trituration with sodium hydrogen carbonate, left *1-acetyl-2-hydroxyxanthone* as pale-yellow needles (0·61 g) (ethanol), m.p. 237°, identical with the insoluble substance A (see above) λ_{max} 237 (35,700), 303 (3600), 366 (6700) (Found: C, 71·0; H, 4·0. $C_{15}H_{10}O_4$ requires C, 70·9; H, 4·0%). It had a negative ferric reaction and gave no precipitate with Brady's reagent. Its *acetyl* derivative obtained from acetic anhydride and pyridine or by the boric acid-acetic anhydride method crystallised as white needles (ethanol), m.p. 160° (Found: C, 69·2; H, 4·2. $C_{17}H_{12}O_5$ requires C, 68·9; H, 4·1%). Its *methyl ether* prepared with dimethyl sulphate had m.p. 185° λ_{max} 238 (41,800), 300 (3600), 363 (6900) (Found: C, 71·5; H, 4·6. $C_{16}H_{12}O_4$ requires C, 71·6; H, 4·5%).

(b) 3-Acetyl-2′-carboxy-4-hydroxydiphenyl ether (see next experiment) (2·72 g), aluminium chloride (6·92 g), and acetyl chloride (1·72 g) in carbon disulphide (50 ml) were heated under reflux with agitation for 3 hr and then set aside over-night. After decantation of the solvent the residue was worked up in the usual way yielding 1-acetyl-2-hydroxyxanthone (37%).

3-Acetyl-2′-carboxy-4-hydroxydiphenyl ether

The sodium hydrogen carbonate extract of the previous experiment described under (a) gave on acidification a gum (5·2 g) which was separable into two components as follows: recrystallisation of the residue (aqueous ethanol) followed by extraction with petroleum ether (b.p. 100–120°) left a *2′-carboxydiacetyl-4-hydroxydiphenyl ether* (1·8%), m.p. 209° (Found: C, 65·2; H, 4·6. $C_{17}H_{14}O_6$ requires C, 65·0; H, 4·5%). It gave a green ethanolic ferric reaction and an orange precipitate with Brady's reagent. From the petroleum ether extract *3-acetyl-2′-carboxy-4-hydroxydiphenyl ether* (5·4%) was obtained as white crystals, m.p. 172°, identical with the hydrolysis product from the ethyl ester described above (Found: C, 66·2; H, 4·5. $C_{15}H_{12}O_5$ requires C, 66·2; H, 4·4%). It gave a positive reaction with Brady's reagent and a dark-green ethanolic ferric reaction.

Action of polyphosphoric acid on 3-acetyl-2′-carboxy-4-hydroxydiphenyl ether

(a) *Reaction temperature* 55°. The ether (0·68 g) and *poly*phosphoric acid (made from 1·9 g P_2O_5 and 1·6 ml syrupy phosphoric acid) were heated at 55° for 0·5 hr with occasional stirring. On diluting the reaction mixture with water (50 ml) only starting material was recovered.

(b) *Reaction temperature below* 80°. A reaction mixture similar to that under (a) was heated between 60–70° for 0·5 hr, water (50 ml) added and the precipitate extracted

several times with chloroform and sodium hydrogen carbonate. The insoluble residue proved to be 1-acetyl-2-hydroxyxanthone (31%). The sodium hydrogen carbonate extract yielded starting material. From the chloroform layer a yellow substance was obtained on evaporation which was not further investigated.

(c) *Reaction temperature above* 80°. A reaction mixture as described under (a) was heated for 1 hr between 90–110°. Extraction of the insoluble residue, obtained by addition of water, with sodium hydrogen carbonate left some 2-hydroxyxanthone. Acidification of the alkaline extract (hydrochloric acid) precipitated *phosphono-2-oxyxanthone* as small white needles (acetic acid) (Found: C, 53·0; H, 3·2; P, 10·5. $C_{13}H_9O_6P$ requires C, 53·4; H, 3·1; P, 10·6%). Its m.p. remained at 226–227° on admixture with a specimen prepared unambiguously by heating polyphosphoric acid and 2-hydroxyxanthone for 1 hr at 110°.

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Action of polyphosphoric acid on 1-*acetyl*-2-*hydroxyxanthone*

A mixture of polyphosphoric acid (from P_2O_5 1·9 g, and syrupy phosphoric acid 1·6 ml) and the ketone (0·63 g) was heated at 110° for 1 hr. The precipitate obtained by pouring the reaction mixture into water yielded 2-hydroxyxanthone and phosphono-2-oxyxanthone separable with sodium hydrogen carbonate.

Reaction of 1-*formyl*-2-*hydroxyxanthone with diazomethane*

To an ice-cold solution of 1-formyl-2-hydroxyxanthone (0·60 g) in chloroform (ethanol free; 70 ml) an ethereal solution of diazomethane (0·11 g in 20 ml ether) was added in one portion and set aside for 24 hr in the dark. From the precipitate 2-*hydroxy*-9-*oxo*-1-*xanthylethylene oxide* (0·1 g) was obtained as white needles (ethanol) m.p. 198–200° (Found: C, 70·5; H, 4·1. $C_{15}H_{10}O_4$ requires C, 70·9; H, 4·0%). A further quantity (0·4 g) of crude oxide resulted from evaporation of the filtrate. The substance had a negative ferric chloride reaction. Its *acetyl* derivative was prepared by the acetic anhydride-pyridine method as white needles, m.p. 211° (Found: C, 68·8: H, 4·1. $C_{17}H_{12}O_5$ requires C, 68·9; H, 4·1%).

Furano(3′:2′–1:2)*xanthone*

A suspension of the above hydroxyethylene oxide (0·02 g) in 2 N-sulphuric acid (10 ml) was refluxed for 5 min, cooled, and filtered. Removal of starting material from the precipitate by extraction with 2 N-sodium hydroxide left furano(3′:2′–1:2)xanthone (0·01 g) λ_{max} 233 (25,800), 250 (23,100), 305 (11,000), 351 (9800), m.p. 144°, undepressed on admixture with an authentic sample.[10]

2-*Acetoxy*-1-*carboxyxanthone*

To a solution of 2-acetoxy-1-formylxanthone[10] (1·4 g) in boiling acetone (200 ml) finely powdered potassium permanganate (2·5 g) was added over 1 hr. After addition of water (100 ml) sulphur dioxide was passed through the reaction mixture and the solvent was driven off. The residue was collected and taken up in chloroform (50 ml). Acidification of a sodium hydrogen carbonate extract gave 2-*acetoxy*-1-*carboxyxanthone* (41%) as white needles (ethanol), m.p. 172–5° (decomp) (Found: C, 64·7; H, 3·3. $C_{16}H_{10}O_6$ requires C, 64·4; H, 3·4%). Hydrolysis (2 N-sodium hydroxide) furnished 1-*carboxy*-2-*hydroxyxanthone* as yellow needles, (benzene) m.p. 185–186°

(decomp) (Found: C, 65·4; H, 3·2. $C_{14}H_8O_5$ requires C, 65·6; H, 3·1%). When 2-acetoxy-1-carboxyxanthone (0·5 g) was heated with thionyl chloride (1·0 g) in dry benzene (40 ml) at reflux temperature for 0·5 hr a crude, unstable acid chloride m.p. 160–165° (decomp) was obtained. It gave *2-acetoxy-1-ethoxycarbonylxanthone* when refluxed in ethanol as white needles, m.p. 190° (Found: C, 66·1; H, 4·3. $C_{18}H_{14}O_6$ requires C, 66·3; H, 4·3%). An unidentified pale-yellow solid, m.p. 175–190° was obtained when the acid chloride was made to react with diazomethane. From the reaction of the acid chloride with dimethylcadmium only 1-carboxy-2-hydroxyxanthone could be isolated.

1-Carboxy-2-methoxyxanthone

1-Formyl-2-methoxyxanthone was prepared from dimethyl sulphate and 1-formyl-2-hydroxyxanthone as white needles, m.p. 207° (ethanol) (Found: C, 70·9; H, 3·9. $C_{15}H_{10}O_5$ requires C, 70·8; H, 4·0%). The methoxy-compound (0·1 g) was oxidised in refluxing acetone (25 ml) with powdered potassium permanganate (0·18 g) and worked up as described for 2-acetoxy-1-carboxyxanthone. *1-Carboxy-2-methoxyxanthone* was obtained as white needles (66%) m.p. 246° (decomp) (Found: C, 66·6; H, 3·9. $C_{15}H_{10}O_5$ requires C, 66·7; H, 3·7%).

Oxidation experiments with 1-acetyl-2-hydroxyxanthone

(a) Conventional Dakin reactions (in pyridine or aqueous sodium hydroxide), oxidation of the ketone in pyridine with iodine, or by hypobromite or treatment of 1-acetyl-2-methoxyxanthone with potassium permanganate in pyridine gave starting material only. In a modified hypobromite oxidation,[8] to a suspension of the ketone (0·27 g) in dioxan (8 ml) an ice-cold mixture of potassium hydroxide (0·5 g), water (2·5 ml) and bromine (0·5 g) was added dropwise and stirred at room temperature for 1 hr. Crystallisation (ethanol) of the resulting white precipitate afforded *1-tribromoacetyl-2-methoxyxanthone* (74%) as plates, m.p. 204° (Found: C, 38·4; H, 1·9; Br, 47·4. $C_{16}H_9O_4Br_3$ requires C, 38·0; H, 1·8; Br, 47·5%). Hydrolysis of the bromoketone (aqueous potassium hydroxide, 8%) gave mainly starting material.

(b) 1-Acetyl-2-methoxyxanthone (0·1 g) in concentrated sulphuric acid (3 ml) was oxidised with chromium trioxide (0·1 g) at −5° with stirring for 1 hr. The mixture was then diluted with water (50 ml) and the precipitate collected. Extraction of the residue with sodium hydrogen carbonate, followed by acidification of the extract, yielded 1-carboxy-2-methoxyxanthone, m.p. and mixed m.p. 244–245°.

4′:5′-Dihydro-4′-oxofurano(3′:2′ 1:2)xanthone

To 1-acetyl-2-hydroxyxanthone (0·25 g) in acetic acid (25 ml) kept at 60° was added a solution of bromine (0·16 g) in acetic acid (10 ml) in one portion. When by raising the temperature to 75° the reaction mixture had become yellow, it was poured onto ice. The crude tribromoketone (0·27 g) m.p. 147–150°, which separated as a yellow precipitate was collected and dried but could not be purified The bromo compound (0·8 g) was refluxed in ethanol (600 ml) in presence of sodium acetate (0·8 g) for 0·75 hr. After treatment with charcoal most of the solvent was removed and 4′:5′-dihydro-4′-oxofurano(3′:2′–1:2)xanthone (0·40 g) was precipitated by addition of water. It crystallised as needles (ethanol), m.p. 208°, λ_{max} 229 (29,500), 250 (30,900), 300 (3000),

358 (9500) (Found: C, 71·2; H, 3·4. $C_{15}H_8O_4$ requires C, 71·4; H, 3·2%). It gave a precipitate with Brady's reagent.

4′-Methylfurano(3′:2′–1:2)xanthone

1-Acetyl-2-hydroxyxanthone (1·02 g), ethyl bromoacetate (1·01 g) and anhydrous potassium carbonate (2·76 g) were boiled under reflux with acetone (30 ml) for 0·5 hr. The filtrate from the reaction mixture yielded after removal of the solvent a pasty residue which afforded *ethyl-1-acetyl-9-oxo-2-xanthyloxyacetate* (95%) as white needles from ethanol, m.p. 151° (Found: C, 67·1; H, 4·6. $C_{19}H_{16}O_6$ requires C, 67·0, H, 4·7%). Hydrolysis with 2 N-sodium hydroxide gave the *acid* m.p. 210° (decomp) (Found: C, 65·3; H, 3·7) $C_{17}H_{12}O_6$ requires C, 65·4; H, 3·9%). The acid (0·3 g) and sodium acetate (0·75 g) were boiled under reflux in acetic anhydride with stirring for 2 hr. The crude product obtained by the procedure described for the parent compound[10] gave *4′-methylfurano(3′:2′–1:2)xanthone* as white needles from ethanol, λ_{max} 235 (27,300), 318 (9600), 354 (10,600), m.p. 137° (Found: C, 76·8; H, 3·9. $C_{16}H_{10}O_3$ requires C, 76·8; H, 4·0%).

6′-Ethoxycarbonyl-4′-pyrono(3′:2′–1:2)xanthone

1-Acetyl-2-hydroxyxanthone (0·5 g), sodium ethoxide (0·3 g), diethyl oxalate (0·44 g) and xylene (40 ml) were heated and agitated on a steam-bath for 3 hr. Filtration of the reaction mixture gave a residue which was acidified (dilute hydrochloric acid) and then extracted with chloroform (25 ml). The chloroform layer was then repeatedly extracted with aqueous sodium hydrogen carbonate (3 × 10 ml). Acidification of the precipitate formed during this extraction yielded a white substance (0·16 g), m.p. 100–110°. On boiling it with a mixture of ethanol (8 ml) and concentrated hydrochloric acid (0·4 ml) for 10 min a pale-yellow precipitate was produced which gave *6′-ethoxycarbonyl-4′-pyrono(3′:2′–1:2)xanthone* from ethanol, m.p. 252–253° (decomp) λ_{max} 218 (26,000), 273 (20,500), 346 (6500), 362 (6500) (Found: C, 67·8; H, 3·8. $C_{19}H_{12}O_6$ requires C, 67·8; H, 3·6%). Hydrolysis of the ester (hydrochloric acid and acetic acid) furnished the *acid hydrate*, m.p. 202–203° (decomp) λ_{max} 221 (24,600), 275 (20,700), 313 (6500), 345 (6000), 360 (6200) (Found: C, 63·0; H, 3·4. $C_{17}H_{10}O_7$ requires C, 62·5; H, 3·1%).

5′-Benzoyl-6′-phenyl-4′-pyrono(3′:2′–1:2)xanthone

1-Acetyl-2-hydroxyxanthone (0·51 g), benzoic anhydride (2·7 g) and sodium benzoate (0·58 g) were heated at 180–190° in an air-bath for 6 hr. The reaction product was then boiled with 2 N-sodium hydroxide (10 ml) for 0·5 hr and extracted with chloroform (15 ml). Evaporation of the solvent and repeated crystallisation (ethanol) of the resulting residue gave *5′-benzoyl-6′-phenyl-4′-pyrono(3′:2′–1:2)xanthone* as pale-pink needles, m.p. 280° (Found: C, 78·3; H, 4·2. $C_{29}H_{16}O_5$ requires C, 78·4; H, 3·6%).

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THE STRUCTURE OF PERIPLANETIN*

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Abstract—The crystalline substance, $C_{13}H_{16}O_7$ periplanetin, isolated from the secretion of the laterocervical organ of *Periplaneta americana* L. and *Blatta orientalis* L., is 1-*benzoyl*-β-D-*glucose*, (II) whose occurrence in nature has not hitherto been reported.

As previously reported,[1] the solid secretion of the laterocervical organ of some Blattidae (*Periplaneta americana L., Blatta orientalis L.*) contains a crystalline white substance designated *periplanetin*. From 1000 insects (males and females) of *P. americana* weighing 880 g, 40–50 mg of the pure product can be isolated.

Periplanetin crystallises from water in small white prisms, melts undecomposed at 193°, is neutral and shows a blue-whitish fluorescence at the Wood's light. Its molecular formula is $C_{13}H_{16}O_7$. Because of the difficulty in obtaining starting material, which is isolated from fresh insects by a tedious process, a study of the infra-red spectrum of the pure substance was undertaken before any chemical investigation.

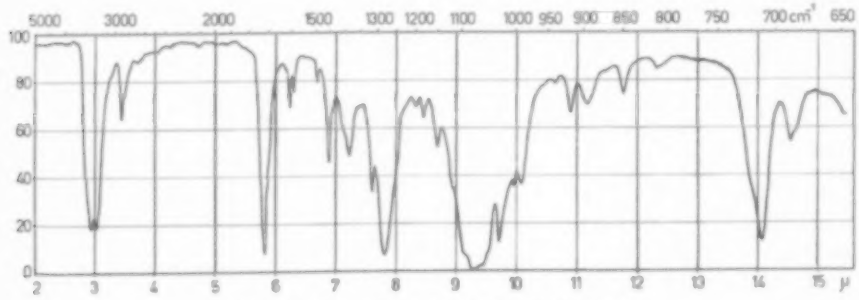


FIG. 1. I.R. spectrum of periplanetin (in KBr).

The *infra-red spectrum* of periplanetin in KBr (Fig. 1) shows in the 3500–3200 cm^{-1} region a strong and complex band assignable to OH groups and this is supported by the presence of a broad band at 1100–1050 cm^{-1}. The existence of a limited number of CH_2 groups is suggested by the occurrence of the bands at 2920, 2860 and 1450 cm^{-1}, whereas the lack of absorption in the 2960 cm^{-1} region indicates that CH_3 groups are not present. The existence in periplanetin of aromatic nuclei is clearly demonstrated by a number of characteristic absorptions; such as the three bands in the 1600–1500 cm^{-1} region, the intense band at 710 cm^{-1}, and some weak bands in the 1250–950 cm^{-1} region. Moreover, the intensity of the doublet at 1604 and 1585 cm^{-1} suggests a conjugation of the benzene ring with other unsaturated groups. There are two strong

* Communication presented at the VIII National Congress of the Società Chimica Italiana held jointly with the Society of Chemical Industry, Turin, May 1958. Abstracts of Congress, B. 175.

[1] M. Pavan, *Boll. Soc. Ital. Biol. Sperim.* **30**, 873, 875 (1954).

bands at 1715 and 1279 cm^{-1}; the first, on account of its position and intensity, may be assigned to the C=O and the second to the C—O stretching vibration of an aromatic ester, confirmed by the intense band at 1100 cm^{-1} which appears on the side of the broad band due to the alcoholic C—O.

From the above data and a comparison of the frequencies of the characteristic bands in i.r. spectra of periplanetin and some benzoic esters (Table 1),[2] it may be safely concluded that periplanetin is the benzoate of a polyhydroxylated compound which still contains free OH groups in its molecule.

TABLE 1. FREQUENCIES (cm^{-1}) OF THE CHARACTERISTIC BANDS IN I.R. SPECTRA OF PERIPLANETIN AND SOME BENZOATES

Compound	C=O	Aromatic ring			C—O		Aromatic CH
Methyl benzoate	1725	1607	1585	1496	1277	1108	707
Ethyl benzoate	1725	1608	1588	1497	1277	1108	709
iso-Propyl benzoate	1715	1608	1588	1492	1274	1108	708
iso-Pentyl benzoate	1725	1609	1590	1496	1274	1111	708
Periplanetin	1715	1604	1585	1493	1279	1100	710

Taking into account its molecular formula, periplanetin must, therefore be a *monobenzoyl-hexose*, $C_6H_5CO\text{–}OC_6H_{11}O_5$. Accordingly, on short heating with 12% HCl on the water-bath, periplanetin affords a crystalline acid m.p. 121° which is identical with *benzoic acid*. The aqueous solution, evaporated *in vacuo* at ordinary temperature after removal of benzoic acid, leaves a glassy residue which readily reduces Fehling's solution.

Owing to the difficulty of obtaining a crystalline product from the small quantity of substance available, the identification of the sugar moiety in periplanetin was performed by paper chromatography. The experiments summarised in Table 2 indicate that the hexose formed from the hydrolysis of periplanetin is D-*glucose*.

Periplanetin is, therefore, a *benzoyl*-D-*glucose* in which configuration and position of the benzoyl group is still to be confirmed. Since benzoic acid is formed on treatment

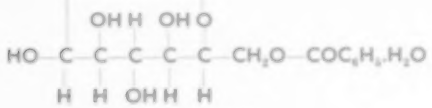
TABLE 2. PAPER CHROMATOGRAPHY OF THE SUGAR FROM PERIPLANETIN AND OF NATURAL HEXOSES

Hexose	Eluent butanol–pyridine–water 6:4:3 R_f	Eluent butanol–acetic acid–water 4:1:5 R_f	Eluent ethyl acetate–pyridine–water 10:4:3 R_f
D-Galactose	0·34	0·20	0·46
D-Glucose	0·38	0·20	0·52
Sugar from periplanetin	0·38	0·20	0·52
D-Fructose	0·42	0·23	0·59
D-Mannose	0·43	0·23	0·57

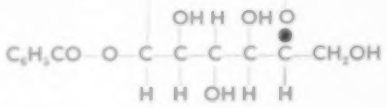
[2] *D.M.S. Spectral Cards* No. 1043, 1241, 1044 and 1045.

of the substance with *emulsin* in the presence of calcium carbonate, periplanetin is most probably a *β-glucoside*.

Only two D-glucose *mono*benzoylderivatives have been reported in the literature, namely, 6-*benzoyl*-D-*glucose* or *vacciniin* (I), originally isolated from the juice of the bearberry (*Vaccinium vitis idea*. L.)[3] and synthesised by Fischer and North;[4] 1-*benzoyl*-*β*-D-*glucose* prepared by Zervas[5] but not found in nature. Periplanetin is not vacciniin (which contains a molecule of water and melts at 104–106°), but could be identical with Zervas' 1-benzoyl-*β*-D-glucose, which also melts at 193° and does not form a hydrate. Further, *tetraacetylperiplanetin* m.p. 140°–141° may be identical with 1-benzoyl-*β*-D-glucose tetraacetate,[5] m.p. 145°.



I. Vacciniin



II. Periplanetin

That periplanetin is actually 1-benzoyl-*β*-D-glucose has been proved by synthesis[5] (benzoylation of 4:6-benzylidene-α-D-glucose followed by catalytic hydrogenolysis of the benzylidene derivative). Synthetic periplanetin melts at 191° undecomposed and the m.p. is not depressed on mixing with the natural product. The *infra-red spectra* of natural periplanetin and synthetic 1-benzoyl-*β*-D-glucose as well as those of the correspondirg tetraacetates reported in Fig. 2, also confirm the identity of the two substances.

Althovgh the occurrence of aromatic 1-esters of D-glucose in plants had been reported,* no example was known of the isolation of substances of this type from animal orgınisms. The function of periplanetin in the insect's economy is still unknow but it seems possible that it may represent the form in which benzoic acid is excreted from the orgınism.

EXPERIMENTAL

Extraction and purification of periplanetin. The crude product was obtained by scraping the material deposited on the surface of the insect's neck and by removing the gland by which the substance is secreted.† From about 3000 insects of *Periplaneta americana* L., 0·462 g of material were collected. The coarse grey powder thus obtained, which contains mechanical impurities (hairs, fragments of cuticle etc.) was suspended in 20 ml of water at 35°–40°, filtered and the clear solution, after extraction with peroxide-free ether, was decolorised with Norit. From the ethereal layer 55 mg of a crystalline acid m.p. 120–121° identical with benzoic acid were obtained.

The aqueous solution, dried *in vacuo* over P_2O_5 and KOH, gave 230 mg of a white crystalline residue which was purified by repeated recrystallisation from water. In total 150 mg of fairly pure periplanetin were isolated. In the mother liquors some free sugar was present (aniline phtalate test).

* Glucogallin, found in Chinese rhubarb, is 1-galloyl-*β*-D-glucose. See: E. Gilson, *Bull. Acad. Roy. Méd. Belg.* 4, **16**, 837, 842, 851 (1902); E. Fischer and M. Bergmann, *Ber. Dtsch. Chem. Ges.* **51**, 1766 (1918).

† The location of the product is rendered evident by the intense blue-whitish fluorescence at the Wood's light.

[3] C. Griebel, *Chem. Zentr.* I, 540 (1910).

[4] E. Fischer and H. Noth, *Chem. Zentr.* I, 488 1917; *Ber. Dtsch. Chem. Ges.* **51**, 326, 330 (1918).

[5] L. Zervas, *Ber. Dtsch. Chem. Ges.* **64**, 2289 (1931).

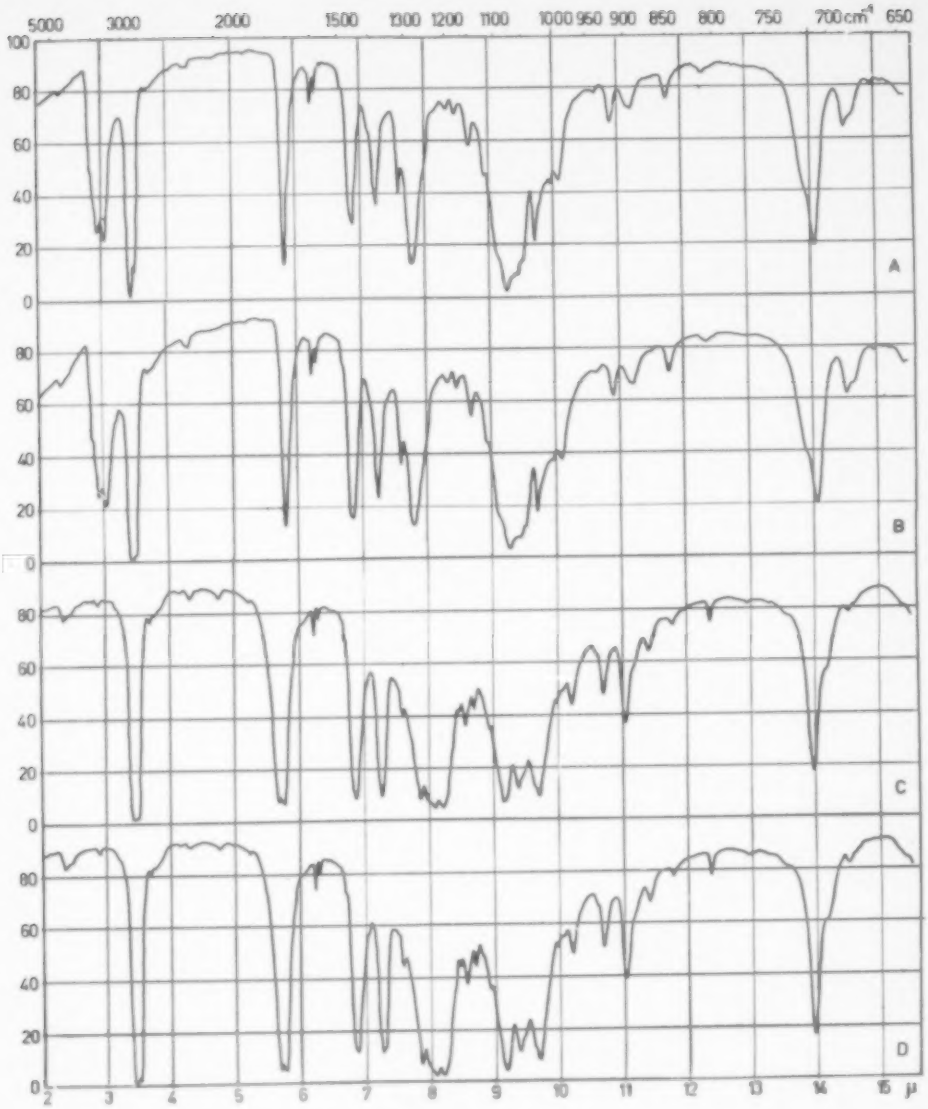


FIG. 2. I.R. spectra in Nujol.
A—Natural periplanetin
B—Synthetic 1-benzoyl-β-D-glucose
C—Tetraacetylperiplanetin
D—Tetraacetyl-1-benzoyl-β-D-glucose

Pure periplanetin forms small silver-white prisms m.p. 193°. It is readily soluble in water, ethanol and methanol, and shows a characteristic blue-white fluorescence at the Wood's light. The i.r. spectrum (in KBr) is reported in Fig. 1. (Found: C, 54·99; H, 6·07. Calc. for $C_{13}H_{16}O_7$: C, 54·93; H, 5·67%).

The product isolated from *Blatta orientalis L.* by the same procedure melted at 193° and possessed an i.r. spectrum identical to that of periplanetin.

Hydrolysis of periplanetin with acids. A solution of periplanetin (50 mg) in HCl (12%, 15 ml) was heated for 5 min on the water-bath, and then evaporated to dryness *in vacuo* at room temperature over P_2O_5 and KOH. The solid residue was dissolved in water and the solution shaken with peroxide-free ether. The ethereal layer on evaporation gave benzoic acid (13 mg) which melted, after sublimation, at 121°. The aqueous solution, treated with Norit and evaporated over P_2O_5 and KOH *in vacuo*, yielded a glassy residue containing the sugar moiety of periplanetin.

The identification of the sugar was performed by paper chromatography (N.1 Whatman paper) using as solvents the mixtures: *n*-butanol–pyridine–water 6:4:3;[6] *n*-butanol–acetic acid–water 4:1:5[7]; ethyl acetate–pyridine–water 10:4:3.[8] After spraying with aniline phthalate solution[9] (*n*-butanol saturated with water 50 ml, phthalic acid 0·83 g, aniline 0·46 g) and heating at 105° for 10 min brown spots which show a yellow-greenish fluorescence at the Wood's light are developed. The values of the R_f reported in Table 2 demonstrate that the sugar formed by hydrolysis of periplanetin is D-glucose.[2]

Enzymatic hydrolysis of periplanetin. Periplanetin (30 mg) dissolved in water, (10 ml) commercial emulsin (Fluka), 80 mg and precipitated $CaCO_3$ (120 mg) were added. After 24 hr at room temperature the mixture was treated with dilute HCl and extracted with ether. The ether layer evaporated gave *benzoic acid* m.p. 120°. In an experiment under the same conditions but in absence of emulsin, no benzoic acid was formed.

Tetraacetylperiplanetin. To a mixture of acetic anhydride (80 mg) and pyridine (60 mg) periplanetin (30 mg) was added. Solution was complete in about 2 hr. After 24 hr at room temperature the crystalline mass was poured into water (2 ml) and the precipitate filtered. After repeated crystallisation from ethanol tetraacetylperiplanetin forms white needles m.p. 140–141°. The i.r. spectrum (Nujol) is shown in Fig. 2, C. (Found: C, 55·10; H, 5·75. Calc. for $C_{21}H_{24}O_{11}$: C, 55·75; H, 5·35%).

Synthetic periplanetin. 1-Benzoyl-β-D-glucose was prepared according to Zervas[5] but it was found that the hydrogenolysis of 1-benzoyl-4:6-D-glucose proceeds better in acetic acid solution than in methanol as suggested by that author. The product, obtained by removal of the solvent *in vacuo* at room temperature and purified by repeated crystallisation from water, formed white prisms m.p. 191°. The mixture with authentic periplanetin melted at 190°. The i.r. spectrum (Nujol) of synthetic periplanetin reported in Fig. 2, B, is identical with that (Fig. 2, A) of the natural product.

Tetraacetyl-1-benzoyl-β-D-glucose, prepared from synthetic periplanetin as above and recrystallised from ethanol, melted at 139–140° and gave no depression mixed with tetraacetylperiplanetin m.p. 140–141°. The i.r. spectrum (Nujol) reported in Fig. 2 D, confirms the identity of the two products.

[6] A. Jeanes, C. S. Wise and R. J. Dimler, *Analyt. Chem.* **23**, 415 (1951).
[7] S. M. Partridge, *Biochem. J.* **42**, 238 (1948).
[8] N. B. Chanda, E. L. Hirst and D. J. Manners, *J. Chem. Soc.* 1957, 1954.
[9] S. M. Partridge, *Nature, Lond.* **164**, 443 (1949).

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SYNTHESIS OF 3β-HYDROXY ANALOGUES OF STEROIDAL HORMONES, A BIOLOGICALLY ACTIVE CLASS OF COMPOUNDS

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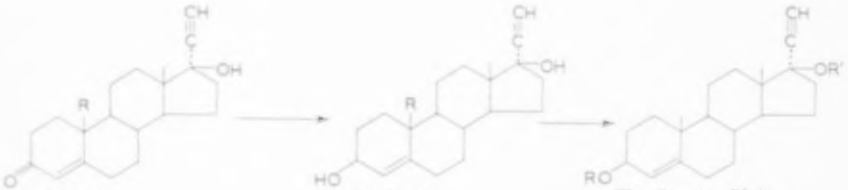
Abstract—Syntheses of 17α-ethinyl-Δ⁴-androstene-3β,17β-diol (IIa), 19-nor-17α-ethinyl-Δ⁴-androstene-3,17β-diol (IIb), Δ⁴-pregnen-3β-ol-20-one (VIa) and Δ⁴-pregnene-3β,21-diol-20-one diacetate (XIX) are described. These 3β-hydroxy analogues of steroidal hormones were found to be biologically active when assayed in animals.

BUTENANDT and Heusner[1] reported in 1938 that Δ⁴-androstene-3β,17β-diol, an analogue of testosterone in which the 3-ketone has been reduced to the 3β-hydroxy-grouping, was a potent androgenic hormone.* In this paper syntheses of the 3β-hydroxy analogues of 17α-ethinyltestosterone, 19-nor-17α-ethinyltestosterone, progesterone and desoxycorticosterone (as the 3,21-diacetate) are described, substances which were found to have high biological activity. Since starting this investigation, the progesterone analogue has also been prepared by Gut[4] who reports it to be a powerful progestational hormone.

17α-Ethinyl-Δ⁴-androstene-3β,17β-diol (IIa) can be prepared simply in 70% yield by reduction of 17α-ethinyltestosterone (Ia) with sodium borohydride in methanol. The spectral properties are in accord with the assigned structure and the retention of the double and triple bonds is confirmed through re-oxidation of (IIa) to the starting material (Ia). The β-configuration of the 3-hydroxy group is to be expected since the reduction of steroidal Δ⁴-3-ketones with sodium borohydride is



Ia; R = Me
b; R = H

IIa; R = Me
b; R = H

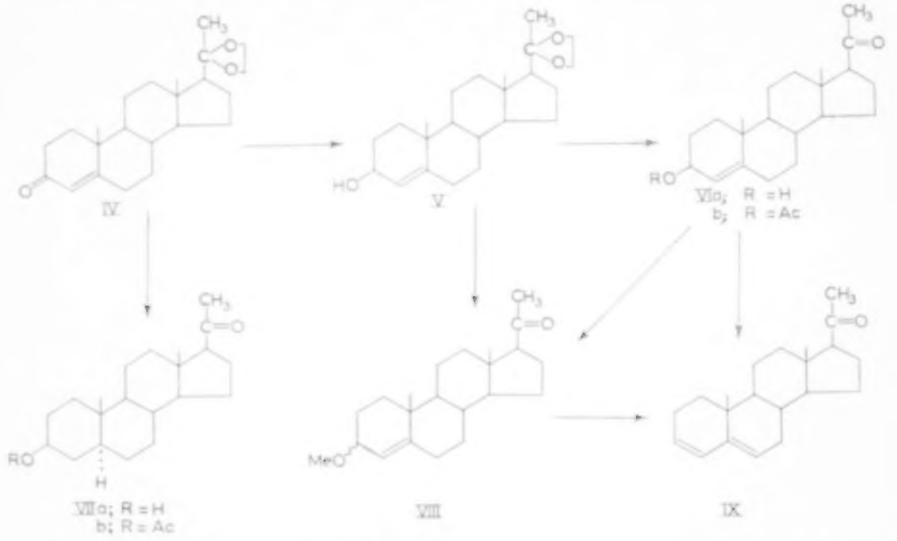
IIIa; R = Ac, R' = H
b; R = R' = Ac

* Quite recently R. I. Dorfman found the corresponding 3,17-diacetate also to have high androgenic activity. This result was reported by S. Bernstein *et al.*[2] who considered it surprising since A. Butenandt in 1935 had stated[3] that the diol exhibited only little activity. However, in 1938 Butenandt[1] reported the result of the previous biological test to have been in error. Further, S. Bernstein *et al.*[2] found that the androgenic activity of 17α-methyl-Δ⁴-androstene-3β,17β-diol, the corresponding analogue of 17-αmethyltestosterone, was of the same order as the parent hormone.

[1] A. Butenandt and A. Heusner, *Ber.* **71**, 198 (1938).
[2] S. Bernstein, S. M. Stolar and M. Heller, *J. Org. Chem.* **22**, 472 (1957).
[3] A. Butenandt, K. Tscherning and G. Hanisch, *Ber.* **68**, 2097 (1935).
[4] M. Gut, *J. Org. Chem.* **21**, 1327 (1956).

known to yield predominantly this isomer,[5] and this assignment is confirmed by molecular rotation considerations (see below). The diol (IIa) was characterised through formation of the 3-monoacetate (IIIa) and the 3,17-diacetate (IIIb).

The analogous reduction of 19-nor-17α-ethinyltestosterone (Ib)[6] with sodium borohydride yielded a non-homogeneous product which only after repeated crystallisation gave an apparently pure substance. The spectral data and elemental analysis show this to be the hydrate of a 19-nor-17α-ethinyl-Δ^4-androstene-3,17β-diol (IIb), but it cannot be said at present whether it is the 3β- or the 3α-isomer or a mixture of the two. The stereochemical course of the metal hydride reduction of 19-nor-Δ^4-3-ketones is unknown and the molecular rotation data do not allow a definite conclusion to be made. The diol (IIb), like the corresponding 19-methyl compound (IIa), does not give an insoluble precipitate with digitonin.



The next objective was the synthesis of Δ^4-pregnen-3β-ol-20-one (VIa). Although pregnane-3,20-dione and *allo*pregnane-3,20-dione can be reduced at C-3 by means of sodium borohydride,[7] the corresponding preferential reduction of progesterone is known to proceed at C-20[8] and cannot, therefore, be used for the preparation of (VIa). The successful method proceeded from progesterone 20-*cyclo*ethylene ketal (IV), readily prepared from Δ^5-pregnen-3β-ol-20-one acetate through successive ketalisation at C-20, saponification at C-3 and Oppenauer oxidation. The details are almost identical to those subsequently described by Gut[4] and are therefore not given in the Experimental Section. The conversion of (IV) to (VIa) depends on finding such acid conditions as will cleave the ketal grouping at C-20 in (V), without causing concomitant dehydration at C-3. After considerable experimentation, it was found that reduction of (IV) with lithium aluminium hydride and

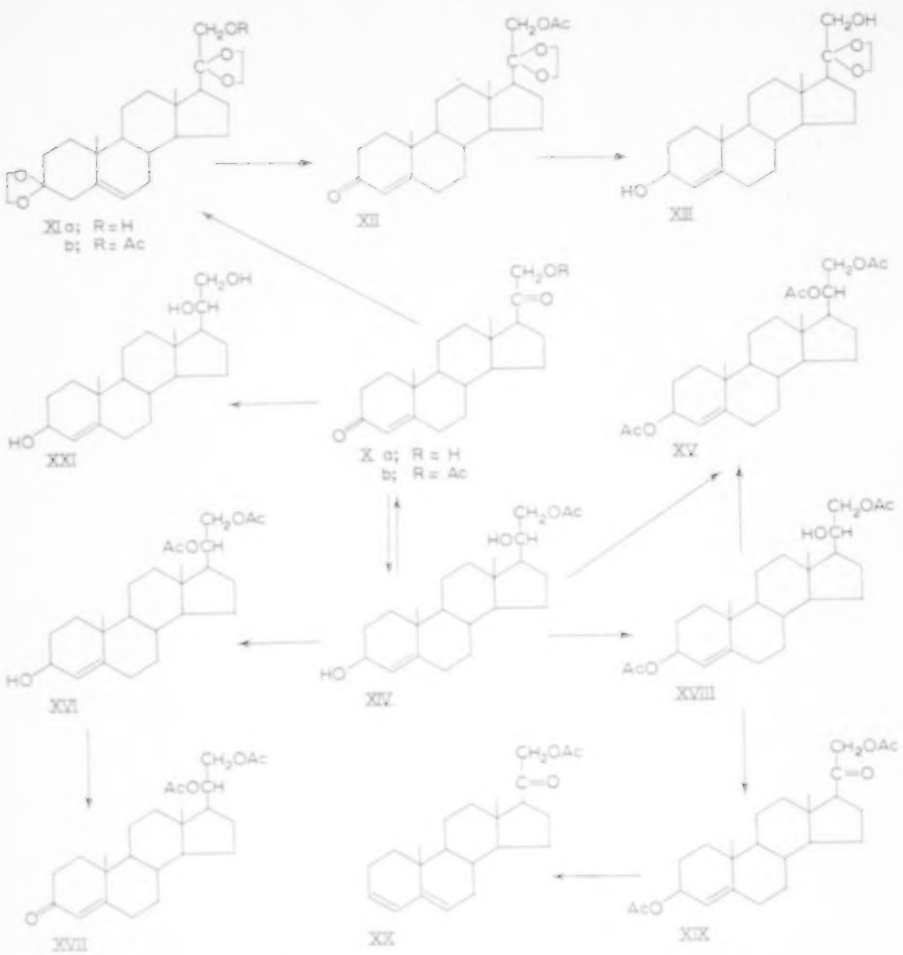
[5] *Cf.* W. G. Dauben, R. A. Micheli and J. F. Eastham, *J. Amer. Chem. Soc.* **74**, 3852 (1952); W. W. Zorbach, *J. Amer. Chem. Soc.* **75**, 6344 (1953).
[6] C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **76**, 4092 (1954).
[7] O. Mancera, H. J. Ringold, C. Djerassi, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **75**, 1286 (1953); A. H. Soloway, A. S. Deutsch and T. F. Gallagher, *Ibid.* **75**, 2356 (1953).
[8] J. K. Norymberski and G. F. Woods, *J. Chem. Soc.* 3426 (1955).

subsequent chromatography gives 64% of (V), which on treatment with *p*-toluenesulphonic acid in ethanol solution at room temperature yields over 90% of (VIa). The structure of the latter was confirmed by acetylation to the acetate (VIb), dehydration to the known $\Delta^{3,5}$-pregnadien-20-one (IX)[9] and oxidation to progesterone. The hydroxy-ketone (VIa) agrees reasonably well in physical properties with the substance reported by Gut[4] by sodium borohydride reduction of the ketal (IV) and treatment of (V) with oxalic acid in ethanol. A comparative experiment showed our acid cleavage conditions to be preferable and to result in a purer product without chromatography.

Prior to the successful synthesis of the hydroxy-ketone (VIa), progesterone 20-*cyclo*ethylene ketal (IV) was reduced with sodium borohydride in aqueous ethanol and the product treated with *p*-toluenesulphonic acid in acetone. This interchange method has been found in other cases to result in the smooth conversion of *cyclo*-ethylene ketals to the parent ketones.[10,17] Three ketonic substances resulted, the first of which was $\Delta^{3,5}$-pregnadien-20-one (IX).[9] The other two substances (only one of which gave a precipitate with digitonin) apparently both possess the empirical formula $C_{21}H_{32}O_2$. It was at first thought that they were the expected 3β- and 3α-isomers of Δ^4-pregnen-3-ol-20-one, but this proved incorrect. The compound precipitated with digitonin is unaffected by manganese dioxide at room temperature,[11] (3β-hydroxy group not allylic) and was shown to be *allo*pregnan-3β-ol-20-one (VIIa) by direct comparison of its acetate with an authentic sample of *allo*pregnan-3β-ol-20-one acetate (VIIb). Sodium borohydride reduction of the Δ^4-3-ketone (IV) results, therefore, partly in the saturation of the double bond, a phenomenon which has been observed previously in another series.[12] Lithium aluminium hydride reduction of Δ^3-3-ketones is reported[12] not to cause any appreciable attack on the double bond and in fact treatment of (IV) with this reagent and subsequent treatment of the total product with *p*-toluenesulphonic acid in acetone gives a mixture of (IX) and the substance giving no precipitate with digitonin.

The last-mentioned substance appears to be a transformation product of (VIa), since it is also obtained by treatment of (VIa) with *p*-toluenesulphonic acid in acetone. It possesses a 20-keto group (infra-red), a double bond (yellow colour with tetranitromethane), and it does not contain a free 3-hydroxyl function. It is converted to (IX) by hydrochloric acid in boiling methanol. After further experimentation it was found that the substance contains a methoxyl group (Zeisel determination) and that it is obtained in increased yield when the hydroxy-ketal (V) or the hydroxy-ketone (VIa) are treated with *p*-toluenesulphonic acid in methanol. It appears to be 3-methoxy-Δ^4-pregnen-20-one (VIII), its formation presumably being due to the presence of a small amount of methanol in the acetone employed. It is of interest that the reaction of the hydroxy-ketal (V) with *p*-toluenesulphonic acid in ethanol gives no appreciable amount of the corresponding ethyl ether. The β- and what may be the α-isomer of the 3-methoxy-Δ^4-ethylene in the cholesterol series have been described recently.[13] The

[9] J. Romo, M. Romero, C. Djerassi and G. Rosenkranz, *J. Amer. Chem. Soc.* **73**, 1528 (1951).
[10] *Cf.* G. Rosenkranz, J. Pataki and C. Djerassi, *J. Org. Chem.* **17**, 290 (1952); G. Rosenkranz, M. Velasco and F. Sondheimer, *J. Amer. Chem. Soc.* **76**, 5024 (1954).
[11] J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *J. Chem. Soc.* 1094 (1952); F. Sondheimer, C. Amendolla and G. Rosenkranz, *J. Amer. Chem. Soc.* **75**, 5930 (1953).
[12] F. Sondheimer, M. Velasco, E. Batres and G. Rosenkranz, *Chem. & Ind.* 1482 (1954).
[13] C. W. Shoppee, B. D. Agashe and G. H. R. Summers, *J. Chem. Soc.* 3107 (1957).



unusually high specific rotation of (VIII) makes it unlikely that it is the pure 3β-isomer; it is probably the 3α-isomer or a molecular compound of the two, but this point has not been investigated. The easy etherification of a Δ^4-3-ol under acid conditions is comparable to the ready etherification of other steroidal allylic alcohols, e.g. of a Δ^5-7-ol (with alcoholic acetic acid)[14] or of a $\Delta^{9(11)}$-ol (with alcoholic hydrogen chloride).[15]

The preparation of Δ^4-pregnene-3β,21-diol-20-one diacetate (XIX), the 3β-acetoxy analogue of desoxycorticosterone acetate, was first attempted by application of the method successfully used in the progesterone series. Desoxycorticosterone (Xa) was converted to the di-*cyclo*ethylene ketal (XIa) and then acetylated, as described previously.[16] Treatment of the resulting ester (XIb) with *p*-toluenesulphonic acid in acetone at room temperature affected only the 3-position, as in the cortisone

[14] *Cf.* H. B. Henbest and E. R. H. Jones, *Nature, Lond.* **158,** 950 (1946); *J. Chem. Soc.* 1798 (1948).
[15] *Cf.* R. B. Turner, V. R. Mattox, L. L. Engel, B. F. McKenzie and E. C. Kendall, *J. Biol. Chem.* **162,** 571 (1946).
[16] S. Bernstein and R. H. Lenhard, *J. Amer. Chem. Soc.* **77,** 2233 (1955).

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series,[17] and yielded the 20-monoketal (XII). Lithium aluminium hydride reduction of the latter gave 80% of the 3β,21-dihydroxy-20-ketal (XIII) which could be regenerated from the insoluble digitonide. Treatment of (XIII) with *p*-toluenesulphonic acid in ethanol at room temperature resulted in the removal of the protecting group at a much slower rate than in the 21-desoxy series and after 6 days only 50% of the product was ketonic, judged from the infra-red spectrum. Chromatographic purification of the resulting material, free or after acetylation, yielded no crystalline material and this method was discontinued when other acid cleavage conditions gave no more promising results.

The successful route to (XIX) involves the reduction of desoxycorticosterone acetate (Xb) with excess sodium borohydride in aqueous tetrahydrofuran at room temperature, conditions which do not affect ester groupings.[18] The product, which no longer showed appreciable ultra-violet absorption, still possessed the 21-acetoxy function (acetyl analysis) and presumably consisted mainly of Δ^4-pregnene-3β,20β,21-triol 21-monoacetate (XIV) as judged from the known predominant formation of β-alcohols by metal hydride reduction of Δ^4-3-ketones[5] and 21-hydroxy-20-ketones.[8] Partial acetylation of this material with a limited amount of acetic anhydride in pyridine yielded a mixture of products from which a triacetate and two diacetates could be obtained by chromatography. The triacetate proved to be Δ^4-pregnene-3β,20β,21-triol triacetate (XV) with properties in excellent agreement with the known compound.[8] One of the diacetates contained the free 3-hydroxy-Δ^4-system since it was oxidised to an unsaturated ketone with manganese dioxide at room temperature and a preparative oxidation with chromium trioxide in pyridine[19] yielded the known[8] Δ^4-pregnene-20β,21-diol-3-one diacetate (XVII). The triol diacetate is therefore Δ^4-pregnene-3β,20β,21-triol 20,21-diacetate (XVI) or the corresponding 3α-isomer.

The second triol diacetate is Δ^4-pregnene-3β,20β,21-triol 3,21-diacetate (XVIII) since acetylation yields the triacetate (XV) and since it is unaffected by manganese dioxide. Oxidation of this diacetate with chromium trioxide in pyridine[19] yields the required Δ^4-pregnene-3β,21-diol-20-one diacetate (XIX). The presence of the 21-acetoxy-20-keto grouping in the latter is shown by the infra-red spectrum (ν_{max} 1748 and 1730 cm^{-1})[20] as well as by the strong red colour given with triphenyltetrazolium chloride,[21] and the Δ^4-3-acetoxy grouping by acid dehydration to the $\Delta^{3,5}$-diene (XX)[9] with its high-intensity ultra-violet maximum at 228 mμ. The β-configuration of the 3-acetoxy group follows from consideration of molecular rotation (see below) and from the fact that (XIX) has been interrelated with the known triacetate (XV).

A variation of the above described route to (XIX) involves the reduction of (Xb) with an excess of lithium aluminium hydride to a mixture of triols, which is acetylated directly with 1·5 moles of acetic anhydride. Chromatography yields a diacetate fraction which on oxidation with chromium trioxide in pyridine and subsequent separation yields (XIX). This partial acetylation yields the 21-monoacetate (XIV) and the corresponding free triol (XXI). The structures of these compounds are based on the fact that both can be acetylated to the triacetate (XV), while oxidation of (XIV) with chromium trioxide in pyridine regenerates (Xb).

[17] F. Sondheimer, O. Mancera, G. Rosenkranz and C. Djerassi, *J. Amer. Chem. Soc.* **75**, 1282 (1953).
[18] H. J. Ringold, B. Löken, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **78**, 816 (1956).
[19] G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *J. Amer. Chem. Soc.* **75**, 422 (1953).
[20] R. N. Jones, P. Humphries, F. Herling and K. Dobriner, *J. Amer. Chem. Soc.* **74**, 2820 (1952).
[21] *Cf.* A. Zaffaroni, *Recent Progress in Hormone Research* **8**, 51 (1953).

In Table 1 the shift in molecular rotation in passing from the Δ^4-3-ketone to the Δ^4-3β-ol (Δ_1) as well as the shift in passing from the Δ^4-3-ketone to the Δ^4-3β-ol acetate (Δ_2) are recorded for the various hormone analogues described in this paper and compared with the known values in the Δ^4-cholesten-3-one and 17α-methyltestosterone series. It can be seen that in all but one case the Δ_1 value is about -200 and the Δ_2 value about -300. This is in marked contrast to the corresponding difference in molecular rotation between the Δ^4-3-ketone and the Δ^4-3α-ol or Δ^4-3α-ol acetate, which is highly positive (Table 1, last line). The one exception is in the 19-nor-17α-ethinyltestosterone series where the Δ_1 value lies about half-way between that expected for the 3β- and for the 3α-ol. It is not known whether this

TABLE 1. MOLECULAR ROTATION DATA OF 3β-HYDROXY- AND 3β-ACETOXY-Δ^4-STEROIDS[a]

Compound	M_D Ketone	M_D 3β-OH	M_D 3β-OAc	Δ_1	Δ_2
Δ^4-Cholesten-3-one	+340[b]	+178[13]	+39[13]	−162	−301
17α-Methyltestosterone	+248[c]	+43[c,d]	−59[d]	−205	−307
17α-Ethinyltestosterone	+122[c,e]	−69[d]	−160	−191	−282
Progesterone	+640[f]	+439	+340	−201	−300
Desoxycorticosterone acetate	+692[f]	—	+408	—	−284
19-Nor-17α-ethinyltestosterone	−75[g]	−124[g]	—	−49	—
	M_D Ketone	M_D 3α-OH	M_D 3α-OAc	Δ_1	Δ_2
Δ^4-Cholesten-3-one	+340[b]	+444[13]	+758[13]	+104	+418

[a] All rotations were determined in chloroform solution unless specified otherwise.
[b] A. Butenandt and A. Wolff, *Ber.* **68**, 2091 (1935).
[c] A. Sandoval, G. H. Thomas, C. Djerassi, G. Rosenkranz and F. Sondheimer, *J. Amer. Chem. Soc.* **77**, 148 (1955).
[d] Determined in methanol.
[e] Determined in chloroform containing 10% of pyridine.
[f] F. Sondheimer, S. Kaufmann, J. Romo, H. Martinez and G. Rosenkranz, *J. Amer. Chem. Soc.* **75**, 4712 (1953).
[g] Determined in ethanol.

anomaly is due to the diol (IIb) actually being an equimolar complex of the two possible isomers as has been observed in the cholesterol series[22] or whether removal of the 19-methyl group changes the Δ_1 value.

*Bioassays.** In the Clauberg assay for oral progestational activity in the rabbit, (IIa) was found to have the same order of activity as 17α-ethinyltestosterone. In the same assay, (IIb) showed the same activity as the potent oral progestational hormone 19-nor-17α-ethinyltestosterone.

On being tested for sodium retention in adrenalectomised male rats, (XIX) showed about the same activity at the 100 and 25 μg level as desoxycorticosterone acetate did at the 25 and 6 μg level, respectively. The analogue (XIX) therefore exhibits ca. 25% of the activity of desoxycorticosterone acetate.

* The biological tests were carried out by the Endocrine Laboratories, Madison 1, Wisconsin, U.S.A.
[22] R. Schoenheimer and E. A. Evans, *J. Biol. Chem.* **114**, 567 (1936).

It still remains to be established whether the Δ^4-3-hydroxy hormone analogues are biologically active *per se* or because of their conversion to the corresponding Δ^4-3-ketones in the organism.

EXPERIMENTAL*

17α-*Ethinyl*-Δ^4-*androstene*-3β,17β-*diol* (IIa)

Sodium borohydride (2·5 g) was added in small portions during 4 hr to a stirred suspension of 17α-ethinyltestosterone (Ia) (5 g) in methanol (200 cc) containing water (0·2 cc). The mixture was allowed to stand overnight at room temperature and was then diluted with water and extracted with chloroform. The organic layer was washed with water, dried and evaporated. Crystallisation from acetone-hexane furnished 3·5 g (70%) of the diol (IIa) with m.p. 207–211°. The analytical sample showed m.p. 211–214°, $[\alpha]_D$ −22° (MeOH), ν_{max} 3300 cm^{-1} (acetylenic hydrogen) and free hydroxyl band, no carbonyl bands, no high intensity absorption in the ultra-violet.

(Found: C, 80·29; H, 9·72; Calc. for $C_{21}H_{30}O_2$: C, 80·21; H, 9·62%.)

The diol gave a yellow colour with tetranitromethane. No precipitate was formed with digitonin in aqueous ethanol. On oxidation with manganese dioxide in dioxane (22°, 24 hr) 17α-ethinyltestosterone m.p. 264–266° was regenerated.

The 3-*monoacetate* (IIIa) was prepared by means of acetic anhydride and pyridine at room temperature. After crystallisation from acetone-hexane it showed m.p. 156–158°, $[\alpha]_D$ −45°, ν_{max} 3300 and 1720 cm^{-1} and free hydroxyl band.

(Found: C, 77·11; H, 8·95; Calc. for $C_{23}H_{32}O_3$: C, 77·49; H, 9·05%.)

The *diacetate* (IIIb) was prepared by boiling the diol (IIa) (315 mg) in pyridine (8 cc) with acetic anhydride (4 cc) for 20 hr. Chromatography of the product followed by crystallisation from hexane gave 290 mg of (IIIb) with m.p. 181–182°, $[\alpha]_D$ −60°, ν_{max} 3300 and 1720 cm^{-1}, no free hydroxyl band.

(Found: C, 75·17; H, 8·84; Calc. for $C_{25}H_{34}O_4$: C, 75·34; H, 8·60%.)

19-*Nor*-17α-*ethinyl*-Δ^4-*androstene*-3,17β-*diol* (IIb)

19-Nor-17α-ethinyltestosterone (1 g)[6] was reduced with sodium borohydride (0·5 g) as described in the preceding experiment. Chromatography of the product on alumina gave 0·81 g of material with m.p. 110–145° which after repeated crystallisation from ether yielded the diol (IIb) as a hydrate with m.p. 147–149°, $[\alpha]_D$ −39° (EtOH), ν_{max}^{KBr} 3300 cm^{-1} and free hydroxyl band, no carbonyl bands, no high-intensity absorption in the ultra-violet. The substance gave no precipitate with digitonin in aqueous ethanol.

(Found: C, 75·26; H, 9·61; Calc. for $C_{20}H_{28}O_2 \cdot H_2O$: C, 75·43; H, 9·50%.)

Δ^4-*Pregnen*-3β-*ol*-20-*one* (VIa)

p-Toluenesulphonic acid hydrate (36 mg) was added to a solution of 400 mg of the pure 3β-hydroxy-ketal (V) (m.p. 168–170°, prepared by lithium aluminium hydride

* Melting points are uncorrected. All chromatograms were carried out with Merck "acid-washed" alumina except for those marked "Alcoa" which were carried out with "Alcoa" activated alumina, grade F-20 (Aluminum Co. of America, Pittsburgh, Pa.). Rotations were determined at room temperature in chloroform solution, unless specified otherwise. Ultra-violet spectra were measured in 95% ethanol solution on a Unicam model S.P. 500 spectrophotometer and infra-red spectra in chloroform solution (unless otherwise stated) on a Baird double beam recording spectrophotometer with sodium chloride optics. Analyses were carried out in our microanalytical laboratory under the direction of Mr. Erich Meier.

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reduction of progesterone 20-*cyclo*ethylene ketal (IV) as described below) in 20 cc of absolute ethanol. The solution was allowed to stand at 23° for 90 min. Sodium bicarbonate solution was then added and the product extracted by means of chloroform. Direct crystallisation from acetone-hexene yielded 320 mg (91%) of pure (VIa), m.p. 159–161°, $[\alpha]_D$ +139°, ν_{max} 1704 cm^{-1} and free hydroxyl band, no high-intensity absorption in the ultra-violet, yellow colour with tetranitromethane, heavy precipitate with digitonin in aqueous ethanol; reported[4] m.p. 155–161° $[\alpha]_D$ +135°.

(Found: C, 79·80; H, 10·02; Calc. for $C_{21}H_{32}O_2$: C, 79·70; H, 10·19%.)

Oxidation of (VIa) with manganese dioxide in chloroform (48 hr at 23°) produced progesterone in over 80% yield. Dehydration of (VIa) with boiling methanol containing a few drops of hydrochloric acid yielded the $\Delta^{3,5}$-diene (IX).

The *acetate* (VIb) (acetic anhydride-pyridine, 16 hr at 22°) crystallised from acetone-hexane, m.p. 125–126°, $[\alpha]_D$ +95°, ν_{max} 1732 and 1704 cm^{-1}, no hydroxyl band.

(Found: C, 77·22; H, 9·47; Calc. for $C_{23}H_{34}O_3$: C, 77·05; H, 9·56%.)

Reduction of progesterone 20-cyclo*ethylene ketal* (IV) *with sodium borohydride followed by treatment with* p-*toluenesulphonic acid in acetone*

Sodium borohydride (2·0 g) was added to a solution of progesterone 20-*cyclo*ethylene ketal (m.p. 190–191°) (2·0 g) in aqueous ethanol (80 cc, 90%). After standing at 23° for 16 hr, the solution was diluted with just sufficient acetic acid to decompose the excess reagent. Water was then added and the product isolated with chloroform. The resultin gmaterial (2·0 g), m.p. 120–150°, has no high-intensity absorption in the ultra-violet, no carbonyl bands in the infra-red. This material was dissolved in dry redistilled acetone (100 cc, commercial grade), *p*-toluenesulphonic acid hydrate (150 mg) added and the solution allowed to stand at 24° for 1½ hr. Sodium bicarbonate solution was then added and the product, extracted by means of ether, chromatographed on 100 g alumina (Alcoa). Elution with benzene-ethyl acetate (99 : 1) and subsequent crystallisation from methanol gave 210 mg (13%) of $\Delta^{3,5}$-pregnadien-20-one (IX), m.p. 138–140°, λ_{max} 228 and 235 mμ, ε = 19,100 and 20,400, respectively; reported:[9] m.p. 139–142°, λ_{max} 228 and 234 mμ, ε = 18,600 and 20,000, respectively. Further elution with benzene-ethyl acetate (99 : 1) and crystallisation from hexane gave 390 mg (21%) of (VIII) with m.p. 147–149°, $[\alpha]_D$ +222°, ν_{max} 1702 cm^{-1}, no appreciable hydroxyl band, no high-intensity absorption in the ultra-violet yellow colour with tetranitromethane, no precipitate with digitionin in aqueous ethanol. (Found: C, 79·80; H, 10·18; OMe, 9·63; act. H, 0·0. Calc. for $C_{22}H_{34}O_2$: C, 79·95; H, 10·37; OMe, 9·39%.)

The substance was recovered unchanged on attempted acetylation with acetic anhydride and pyridine at room temperature. Boiling the ether (VIII, 14 mg) with methanol (1 cc) and conc. hydrochloric acid (2 drops) for 4 hr yielded the diene (IX, 8 mg), m.p. 136–138°, identified by mixed m.p. and the ultra-violet spectrum.

Finally elution with benzene-ethyl acetate (3:1) and crystallisation from acetone-hexane yielded *allo*pregnan-3β-ol-20-one (VIIa, 320 mg, 18%), m.p. 190–192°, $[\alpha]_D$ + 91° (EtOH), no colour produced with tetranitromethane, immediate precipitate with digitonin in aqueous ethanol; reported:[22] m.p. 194·5°, $[\alpha]_D$ +91°

[22] A. Butenandt and L. Mamoli, *Ber.* **68**, 1847 (1935).

(EtOH). The acetate (VIIb) showed m.p. 143–144°, $[\alpha]_D$ +74° and proved to be identical (mixed m.p., infra-red comparison) with an authentic sample (m.p. 142–144°, $[\alpha]_D$ +76°).

Reduction of (IV) *with lithium aluminium hydride followed by treatment with* p-*toluenesulphonic acid in acetone*

A solution of progesterone 20-*cyclo*ethylene ketal (m.p. 190–191°) (2·5 g) in tetrahydrofuran (30 cc) and ether (30 cc) was added during 15 min to a stirred ice-cooled suspension of lithium aluminium hydride (0·8 g) in ether (80 cc) under nitrogen. The mixture was refluxed for 1 hr, the excess reagent decomposed by means of ethyl acetate, and a saturated sodium sulphate solution added until the precipitate began to adhere to the sides of the flask. Solid sodium sulphate was added, the salts removed by filtration and washed well with ether. Evaporation of solvents yielded the crude ketal (V, 2·5 g) showing no high-intensity absorption in the ultra-violet. A 500 mg sample on chromatography on alumina (25 g), followed by elution with benzene-ethyl acetate (9:1) and crystallisation from acetone-hexane, yielded 320 mg (64%) pure 3β-hydroxy-ketal (V), m.p. 168–170°; reported:[4] m.p. 170–173°.

The crude ketal V (2·0 g) in acetone (100 cc) was treated for 1 hr with 150 mg of *p*-toluenesulphonic acid, exactly as described in the preceding experiment. Chromatographic purification of the product yielded first 240 mg (14%) of (IX), m.p. 137–140° and then 580 mg (31%) of (VIII), m.p. 146–148°. No *allo*pregnan-3β-ol-20-one (VIIa) could be isolated.

Treatment of the pure 3β-hydroxy-ketal (V) (m.p. 168–170°) under the same conditions gave 18% of the diene (IX) and 32% of (VIII).

3-*Methoxy*-Δ^4-*pregnen*-20-*one* (VIII) *from* (VIa)

(a) *With* p-*toluenesulphonic acid in acetone.* A solution containing 150 mg of the keto-alcohol (VIa) and *p*-toluenesulphonic acid hydrate (13 mg) in dry redistilled acetone (8 cc, commercial grade) was allowed to stand at 22° for 90 min. The total product, isolated with ether, no longer gave any precipitate with digitonin in aqueous ethanol. Chromatographic purification on alumina (Alcoa) gave 22 mg of the $\Delta^{3,5}$-diene (IX) and then 41 mg of the 3-methoxy-compound (VIII). Both compounds were identified by comparison with the previously described samples.

(b) *With* p-*toluenesulphonic acid in methanol.* The experiment was carried out as above, except that methanol was used instead of acetone and the reaction was allowed to proceed for 8 hr (after 90 min the reaction was incomplete). Chromatographic purification of the product on alumina (Alcoa, 7·5 g) gave (VIII) (91 mg, 58%), m.p. 146–148°, undepressed on admixture with the previously described material.

20-*Ethylenedioxy*-Δ^4-*pregnen*-21-*ol*-3-*one acetate* (*desoxycorticosterone acetate* 20-cyclo*ethylene ketal*) (XII)

A solution containing 120 mg of (XIb) (m.p. 159–161°)[16] and *p*-toluenesulphonic acid hydrate (12 mg) in dry acetone (3 cc) was allowed to stand at 22° for 14 hr. Sodium bicarbonate solution and ether were added, the organic layer was washed with water, dried and evaporated. Crystallisation of the residue from hexane produced

81 mg (75%) of the 20-monoketal (XII), m.p. 140–141°, ν_{max} 1730 and 1660 cm^{-1}, λ_{max} 241 mμ, $\varepsilon = 16{,}600$.

(Found: C, 72·30; H, 8·80; Calc. for $C_{25}H_{36}O_5$ C, 72·08; H, 8·71%.)

20-Ethylenedioxy-Δ^4-pregnene-3β,21-diol (XIII)

A solution of 450 mg of the ketal (XII) in tetrahydrofuran (12 cc) and ether (12 cc) was added slowly under nitrogen to an ice-cooled stirred solution of lithium aluminium hydride (200 mg) in dry ether (30 cc). The mixture was stirred at room temperature for 2 hr, the excess of reagent destroyed by the careful addition of ethyl acetate and saturated sodium sulphate solution added until the precipitate began to adhere to the sides of the flask. Solid sodium sulphate was added, the salts removed by filtration and washed well with ether. The filtrate was evaporated and the residue crystallised from acetone-hexane. This procedure yielded 350 mg (86%) of the 3β,21-diol (XIII), m.p. 199–201°, $[\alpha]_D$ +94° (EtOH), strong hydroxyl but no carbonyl bands in the infra-red, no high-intensity absorption in the ultra-violet.

(Found: C, 73·30; H, 9·93; Calc. for $C_{23}H_{36}O_4$: C, 73·36; H, 9·64%.)

The diol gave a heavy precipitate with digitonin in aqueous ethanol. On regeneration from the digitonide, the diol showed unchanged physical properties.

Reduction of (Xb) *with sodium borohydride followed by partial acetylation*

A solution of sodium borohydride (0·5 g) in water (4 cc) was added to desoxycorticosterone acetate (2·5 g) dissolved in tetrahydrofuran (100 cc). After being allowed to stand at room temperature for 70 hr, the solution was treated with a little acetic acid, evaporated to small volume and diluted with water. Isolation with chloroform gave 2·5 g of the crude triol 21-monoacetate (XIV) as a viscous oil, ν_{max} 1732 cm^{-1} (acetate) and strong hydroxyl band, no band at ca. 1660 cm^{-1}, no high-intensity absorption in the ultra-violet.

(Found: acetyl, 11·24. Calc. for $C_{23}H_{36}O_4$: acetyl, 11·44%.)

The total crude 21-monoacetate (XIV) in dry pyridine (25 cc) was acetylated with acetic anhydride (1·36 g) for 24 hr at room temperature. The product was isolated with ether and chromatographed on alumina (125 g). The first crystalline fractions, eluted with benzene, on crystallisation from acetone-hexane yielded 0·65 g of the triacetate (XV) as needles, m.p. 129–131°, $[\alpha]_D$ +41°, ν_{max} 1732 cm^{-1}, no hydroxyl band; reported:[8] m.p. 128–131°, $[\alpha]_D$ +40°.

(Found: C, 70·56; H, 8·93; acetyl, 29·19; Calc. for $C_{27}H_{40}O_6$: C, 70·40; H, 8·75; acetyl, 28·04%.)

Elution of the column with benzene-chloroform (2:1) gave 1·1 g of a mixture of the diacetates (XVI) and (XVIII). These were separated by a combination of chromatography and fractional crystallisation from acetone-hexane. The required 3,21-diacetate (XVIII) showed m.p. 142–144°, $[\alpha]_D$ +20°, ν_{max} 1732 cm^{-1} and free hydroxyl band.

(Found: C, 71·52; H, 9·20; acetyl, 21·21; Calc. for $C_{25}H_{38}O_5$: C, 71·74; H, 9·15; acetyl, 20·57%.)

The substance in chloroform was unaffected by treatment with manganese dioxide at room temperature for 24 hr. Acetylation with acetic anhydride and pyridine at room temperature quantitatively yielded (XV).

The 20,21-diacetate (XVI) showed m.p. 145–146°, ν_{max} 1734 cm^{-1} and free hydroxyl band, large m.p. depression on mixing with (XVIII).

(Found: C, 71·44; H, 9·36; acetyl, 20·75; Calc. for $C_{25}H_{38}O_5$: C, 71·74; H, 9·15; acetyl, 20·57%.)

The substance contained an allylic alcohol grouping, since treatment with manganese dioxide in chloroform at room temperature for 24 hr resulted in the formation of an αβ-unsaturated ketone (λ_{max} 240 mμ, $\varepsilon = 14{,}000$).

Δ⁴-Pregnene-20β,21-diol-3-one diacetate (XVII)

The 20,21-diacetate (XVI, 80 mg) in pyridine (1 cc) was oxidised with chromium trioxide (100 mg) in pryidine (2 cc) at room temperature for 24 hr. Water was added and the product isolated with ether. Crystallisation from acetone-hexane gave 62 mg of Δ⁴-pregnene-20β,21-diol-3-one diacetate (XVII), m.p. 154–155°, $[\alpha]_D$ +125°, ν_{max} 1736 and 1666 cm^{-1}, no hydroxyl band, λ_{max} 241 mμ, $\varepsilon = 16{,}000$; reported:[8] m.p. 155–156°, $[\alpha]_D$ +123°.

Δ⁴-Pregnene-3β,21-diol-20-one diacetate (XIX)

A solution of 160 mg of the 3,21-diacetate (XVIII) in dry pyridine (2 cc) was added to a mixture of chromium trioxide (200 mg) and pyridine (4 cc). The mixture was allowed to stand at room temperature for 24 hr, diluted with water and extracted with ether. The product was chromatographed on alumina (8 g). Elution with benzene and crystallisation from pentane gave 62 mg of (XIX), m.p. 126–128°, $[\alpha]_D$ +98°, ν_{max} 1748 and 1730 cm^{-1}, no hydroxyl band, no high-intensity absorption in the ultra-violet, strong red colour with triphenyltetrazolium chloride.[21]

(Found: C, 72·16; H, 8·80; Calc. for $C_{25}H_{36}O_5$: C, 72·08; H, 8·71%.)

The presence of the Δ⁴-bond was confirmed by the yellow colour produced with tetranitromethane and by the fact that (XIX) (3 mg) on treatment with *p*-toluene-sulphonic acid (2 mg) in acetone (1 cc) for 1 hr at 60° was dehydrated to the Δ³,⁵-diene (XX) (λ_{max} 228 mμ, $\varepsilon = 17{,}000$).

Reduction of (Xb) *with lithium aluminium hydride followed by partial acetylation*

A solution of 4 g of (Xb) in tetrahydrofuran (100 cc) and ether (100 cc) was added dropwise in nitrogen to a stirred solution of lithium aluminium hydride (1·6 g) in ether (300 cc) with ice-cooling. The mixture was stirred for 90 min at room temperature and then for 20 min under reflux. The excess reagent was decomposed by the careful addition of ethyl acetate, and concentrated aqueous sodium sulphate added until the precipitate began to adhere to the sides of the flask. Solid sodium sulphate was added, the salts removed by filtration and washed well with tetrahydrofuran. Evaporation of solvent under reduced pressure yielded the crude triol (XXI, 3·6 g) showing a hydroxyl band but no carbonyl bands in the infra-red, no high-intensity absorption in the ultra-violet.

The above triol in dry pyridine (68 cc) was acetylated with acetic anhydride (1·65 g, 1·5 equivalents) at −10° for 18 hr. The product was isolated with ether in the usual way and chromatographed on alumina (200 g). Elution with benzene-chloroform (2:1) gave a mixture of diacetates which on direct oxidation with the chromium trioxide-pyridine complex as above, followed by two chromatographic purifications and crystallisation from pentane, yielded 120 mg of (XIX), m.p. 125–127°. The m.p. was not depressed on mixing with the above-described material, and the infra-red spectra were identical.

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Further elution of the column with benzene-chloroform (5:3) gave a monoacetate fraction which on crystallisation from acetone-hexane yielded 1·06 g of the 21-monoacetate (XIV), m.p. 97–99°, $[\alpha]_D$ +46°, ν_{max} 1730 cm^{-1} and free hydroxyl band.

(Found: C, 73·01; H, 9·84; acetyl, 11·38; Calc. for $C_{23}H_{36}O_4$: C, 73·36; H, 9·64; acetyl, 11·44%.)

Acetylation with excess acetic anhydride in pyridine at room temperature quantitatively produced the triacetate (XV), m.p. 129–131°. Oxidation of (XIV) with chromium trioxide-pyridine, as above, and crystallisation of the product from acetone-hexane gave desoxycorticosterone acetate (68%), m.p. 156–158°, λ_{max} 240 mμ, ε = 15,800, ν_{max} 1748, 1736 and 1664 cm^{-1}. The m.p. was not depressed on mixing with an authentic specimen (m.p. 156–158°) and the infra-red spectra were identical.

Finally elution of the column with chloroform-methanol (19:1) produced the thiol (XXI, 0·84 g), needles from acetone, m.p. 162–163°, strong hydroxyl but no carbonyl bands in the infra-red (KBr).

(Found: C, 75·07; H, 10·57; Calc. for $C_{21}H_{34}O_3$: C, 75·40; H, 10·25%.)

The triol gave an immediate precipitate with digitonin in aqueous ethanol. On acetylation, the triacetate (XV) with m.p. and mixed m.p. 129–131° was produced in quantitative yield.

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RESEARCHES ON THE AROMATIC AZOCOMPOUNDS

THE OXIDATION OF THE 4-DIMETHYLAMINO-AZOBENZENE

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Abstract—This paper deals with the oxidation of 4-amino-azobenzene. Mono-oxidation leads to the amine oxide, the structure of which is demonstrated. It is concluded that oxygen adds first to the nitrogen atom with the greater electron density, i.e. the nitrogen of the dimethylamino group, and the second oxygen adds to the azo nitrogen remote from the substituted phenyl group.

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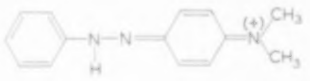
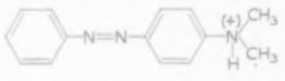
THE position of the first proton in 4-amino-azobenzene derivatives has been long discussed, mainly because of the difficulty to locate the protonated forms existing in solution. It has been assumed that the deepening colour in weakly acidic solution, and the correlated bathochromic shift in the absorption spectra, is due to the formation of an azonium ion and to the contributing resonance structures.

Rogers *et al.*[1] have studied the primary and secondary ionisation constants of 4′-substituted 4-dimethylamino-azobenzenes. These compounds add a proton in dilute acid and a second in strong acidic solutions. The values of p*K*, measured spectrophotometrically, provide evidence that the first proton is added to an azo nitrogen atom (form. I) and the second to the dimethylamino nitrogen atom.



I



II

Badger *et al.*[2] have evaluated the primary ionisation constants of 4-amino-azobenzene and of a number of N-substituted derivatives, and assume that ammonium and azonium forms are in equilibrium in solution, the relative intensities of the Q(5000–5400 Å) and K′(3200 Å) bands giving the approximate proportions of the two tautomers present.

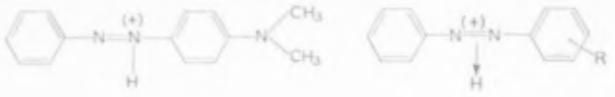
Klotz *et al.*[3] have determined the acidity constants of a number of related substituted azobenzenes, together with some *p*-dimethylamino-phenylazo-pyridines. The results support a structure of the type (II). In aqueous solution the uptake of protons leads to a benzenoid rather than a quinonoid structure and the relative basicities of the possible competing groups lie in the order: $O^- >$ pyridine N $>$ —N$(CH_3)_2 >$ —N=N—.

Miller *et al.*[4] investigated the absorption spectra of ethanolic and acid-ethanolic solutions of a number of derivatives of 4-amino-azobenzene. Their data are in agreement with the results of Hantzsch[5] and Badger,[2] indicating that the first proton can be

[1] M. T. Rogers, T. W. Campbell and R. W. Maatman, *J. Amer. Chem. Soc.* **73**, 5122 (1951).
[2] G. M. Badger, R. G. Buttery and G. E. Lewis, *J. Chem. Soc.* 1 (1954).
[3] I. M. Klotz, H. A. Fiess, J. Y. Chen Ho and M. Mellody, *J. Amer. Chem. Soc.* **76**, 5136 (1954).
[4] G. Cilento, E. G. Miller and J. A. Miller, *J. Amer. Chem. Soc.* **78**, 1718 (1956).
[5] A. Hantzsch and A. Burawoy, *Ber. Dtsch. Chem. Ges.* **63**, 1760 (1930).

added to either the α-azo-nitrogen or the amino nitrogen to give a mixture of tautomeric forms. The work of Miller was recently confirmed and explained quantitatively by Pullman and Pullman.[6]

Sawicki[7] maintained as azonium form the tautomer (III), first suggested by

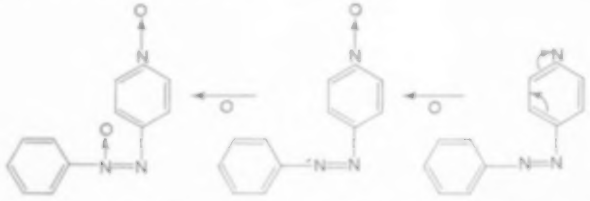


III IV

Sheppard[8] and rejected by Rogers,[1] whilst Jaffé[9] suggested a symmetrical structure of the protonated form of the azo group (form IV).

The problem of the relative basicity of the nitrogen atoms in basic unsymmetrical azocompounds has been approached[10] with particular respect to the heterocyclic unsymmetrical azocompounds, on the basis of some analogies between N-oxidation and N-protonation. The most easily protonated nitrogen, and therefore the nitrogen first protonated in dilute acidic solutions, is the most basic one, with the greater electron density, the lone pair of electrons being easily available, are shared to give a co-ordinate bond with the proton. Similarly, in the N-oxidation, the same pair of electrons on the nitrogen atom will be involved and the extent of availability of the paired electrons will be responsible for the addition of the oxygen atom. On the other hand, the basicity of a nitrogen atom depends on the relative stability of the cation formed by the proton addition; resonance stabilisation is frequently of the same order of importance as electron density in determining their stability. However, the electron density on the nitrogen atoms is a determining factor of the oxygen position and rate control of oxidation. Consequently, sufficient difference among basic nitrogen atoms leads to only one oxidate form, where protonisation often leads to an equilibrium between two forms.

It has been shown, in phenylazo-pyridines and -quinolines, that the mono-oxidation goes toward the nitrogen with highest electron density, to which the first proton adds; thus in the 4-phenylazo-derivatives the first oxygen atom goes to the pyridine nitrogen, to which the first proton adds. In the further oxidation the second

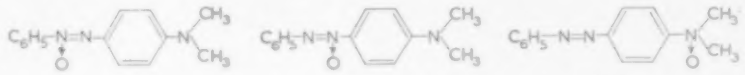


oxygen atom adds to the azo nitrogen farthest from the heterocyclic nucleus (α position), presumably the same azo nitrogen to which the second oxygen adds.

Whereas in the case of the 4-phenylazo-pyridine there is no doubt about the

[6] A. Pullman and B. Pullman, *C.R. Acad. Sci., Paris* **243**, 1322 (1956).
[7] E. Sawicki, *J. Org. Chem.* **22**, 365 (1957).
[8] S. E. Sheppard and P. T. Newsome, *J. Amer. Chem. Soc.* **64**, 2937 (1942).
[9] H. H. Jaffé and R. W. Gardner, *J. Amer. Chem. Soc.* **80**, 319 (1958).
[10] M. Colonna, A. Risaliti and L. Pentimalli, *Gazz. Chim. Ital.* **86**, 1067 (1956).

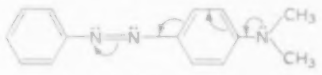
position of the first proton, and consequently of the first oxygen, the position of the first proton in *p*-dimethylamino-azobenzene is not known for certain from previous work.



(V) (VI) (VII)

On the basis of the above assumptions, in the mono-oxidation of Butter Yellow, the α-azoxy (V) and the amino oxide (VII) are the most probable structures.

The structure (VI) seems unlikely, on the basis of Rogers' considerations, supported afterward by Badger *et al.*,[2] who rule out the form (III) protonated on the azo nitrogen closest to the substituted phenyl group. While in the unsubstituted azobenzene the two nitrogens are equivalent, the presence of the dimethylamino grouping in *para* position, with its +I and +M effect, gives rise to an electronic conjugation producing an



VIII

increase of the negative charge on the nitrogen farthest from the amino group.

Both the azoxy compounds (V) and (VI) are reported in literature.[11] The single structure of the two tautomer isomers has been established by Anderson[11] on the basis of their properties, as stability and absorption curves (Fig. 1).

Mono-oxidation of 4-dimethylamino-azobenzene leads almost exclusively to the

VII

N-oxide on the amino nitrogen (VII), the structure of which has been unequivocally demonstrated.

This result is not surprising and it is in agreement with the acidity constant values reported by Klotz *et al.*[3] From the conjugation scheme (VIII) it would seem that the presence of the dimethylamino group should result in a higher basicity for the α-azo nitrogen with respect to the amino nitrogen. Actually, because of the reciprocal effect between the two substituents, $-N(CH_3)_2$ and $-N=N-$, the azo group does become more basic than it is in the unsubstituted azobenzene, while the dimethylamino group becomes less basic with regard to the unsubstituted dimethylaniline; the relative basicity will be still higher for the dimethylamino group which will be thereby oxidised, and protonated, first.

TABLE 1. ACIDITY CONSTANTS, p*Ka*, AT 25°C

Azobenzene[3]		−2·48
Dimethylaniline[12]	6·2–5·5	
p-Dimethylamino-azobenzene[3]	3·5	−4·37

[11] W. Anderson, *J. Chem. Soc.* 1722 (1952).

[12] C. K. Ingold, *Structure and Mechanism in Organic Chemistry* p. 746. Cornell University Press, New York (1953); the higher value has been reported by W. C. Davies and H. W. Addis, *J. Chem. Soc.* 1622 (1937), the lower value by G. Thompson, *J. Chem. Soc.* 1112 (1946).

The observed value of the second acidity constant for the 4-dimethylamino-azobenzene referring to the azogroup, is lower than that of the unsubstituted azobenzene, due to the —I effect of the protonated amino group.

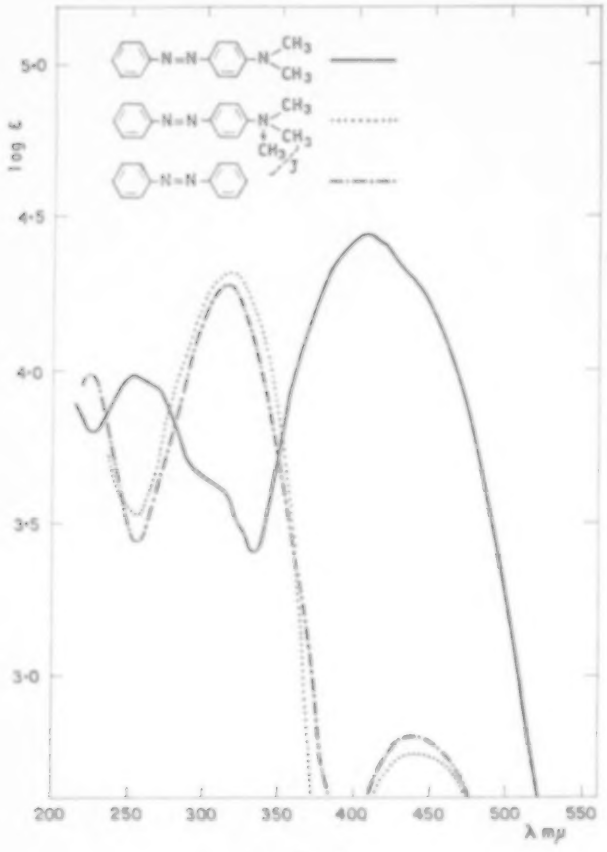


FIG. 1.

Evidence for the structure assigned to the amino-oxide azo (VII) is provided by the following facts:

(a) Analytical data correspond to the formula $C_{14}H_{15}N_3O$, with one more oxygen atom than the *p*-dimethylamino-azobenzene;

(b) The intense orange colour is favourable to the azo structure, the azoxy compounds being markedly less coloured;

(c) The compound is different from the α- and β-azoxy compounds described by Anderson,[11] as to colour, crystal form, solubility and absorption spectrum;

(d) The features of the absorption curve are in agreement with the assigned structure. The values of λ_{max} and related absorption intensities of *p*-dimethylamino-azobenzene and related oxidation derivatives are collected in Table 2.

All of the azocompounds show an absorption band (R band) at about 440 mμ, with

TABLE 2. MAXIMA WAVELENGTH (mμ) AND CORRESPONDING INTENSITIES (log ε) IN THE ABSORPTION SPECTRA OF AZO- AND AZOXY-BENZENES IN ETHANOL

Azobenzene	318 (4·32)		440 (2·73)
Azoxy-benzene trans	322 (4·19)		—
p-Dimethylamino-azobenzene		410 (4·44)	
p-Dimethylamino-azobenzene (methiodide)[13]	319 (4·23)		443 (2·73)
α-Azoxy (V)	410 (4·55)		—
β-Azoxy (VI)	394 (4·49)		—
Amino-oxide-azo (VII)	318 (4·28)		435 (2·78)
Amino-oxide-α-azoxy (X)	321 (4·18)		—

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low intensity (log ε about 2·73), regarded as characteristic for the azo group (Fig. 2); this band is undoubtedly also present in the spectrum of the *p*-dimethylamino-azobenzene but it is hidden by the broad band in the same region, with λ_{max} at 410

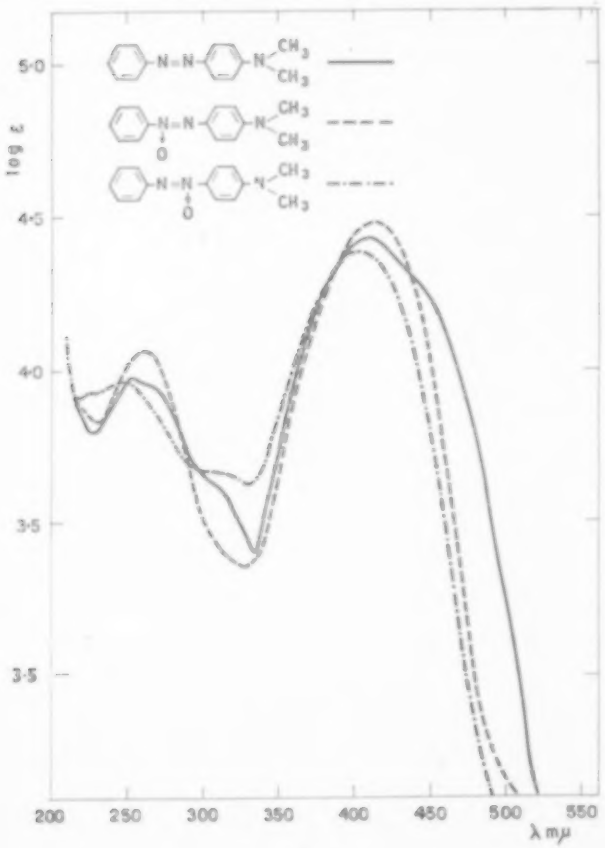


FIG. 2.

[13] A. Pongratz, G. Markgraf and E. Mayer-Pitsch, *Ber. Dtsch. Chem. Ges.* **71**, 1293 (1938).

mμ. With the azoxy-compounds, where the —N = N— group is replaced by the azoxy group, such a band does not appear and it is doubtless absent also for the α- and β- Butter Yellow azoxy derivatives, wherein the corresponding region is covered by the broad conjugation band of the dimethylamino grouping. Evidence

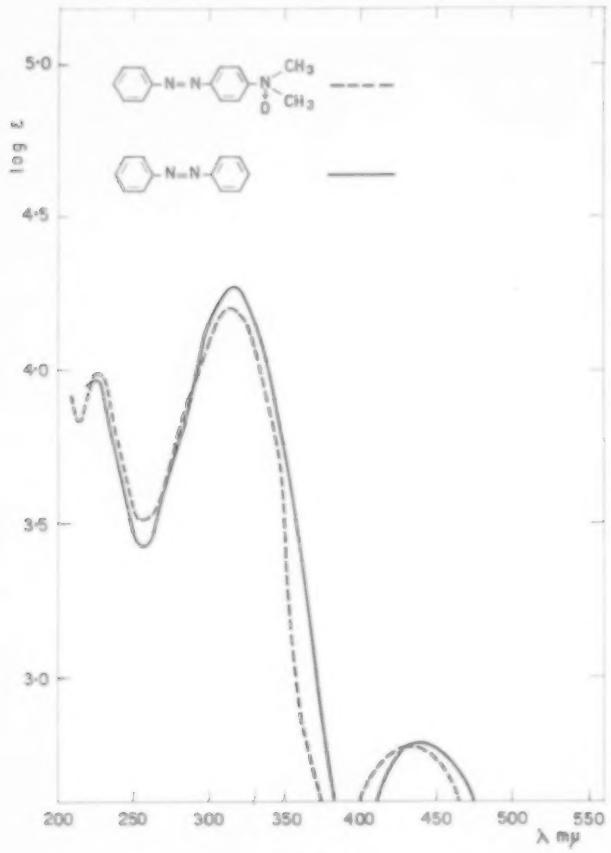


FIG. 3.

for this is provided by the spectra of the azoxybenzene and of the *p*-dimethylamino-azoxybenzenes amino-oxides (IX) and (X), showing no absorption beyond 400 mμ (Fig. 4).

The peak at 435 mμ with a low intensity value, log ε 2·78, for the oxidation compound with suggested structure (VII), indicates clearly the occurence of the —N = N— group.

The amino oxide structure is also supported by the disappearance of the broad intense absorption band at λ_{max} about 410 mμ, associated with the conjugation of the substituent. This is shown by the comparison of the values collected in Table 3: the spectrum of the amino-oxide azo is practically identical to that of the methiodide and therefore identical to that of the unsubstituted azobenzene (Figs. 1 and 3).

TABLE 3. λ_{max} (mμ) AND INTENSITIES (log ε) OF ABSORPTION SPECTRA IN ETHANOL

Azobenzene	229 (4·11)	318 (4·32)	440 (2·73)
p-Dimethylamino- (methiodide)	...	319 (4·32)	443 (2·73)
p-Dimethylamino amino oxide	229 (4·05)	318 (4·28)	435 (2·78)

The conclusion that the first oxygen, in *p*-dimethylamino-azobenzene, goes to the amino nitrogen is consistent with the results reported by Klotz *et al.*, who attribute to the amino group the primary ionisation constant. The question of the absorption

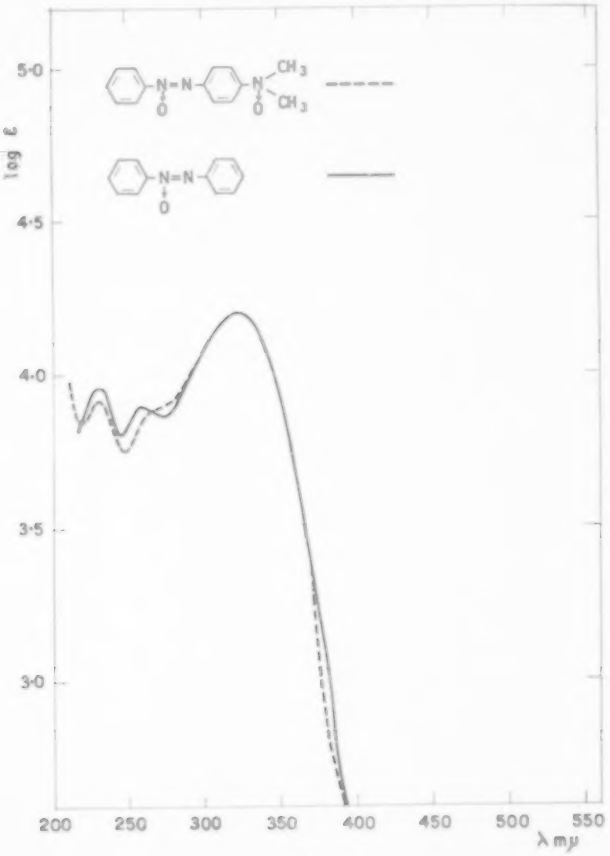
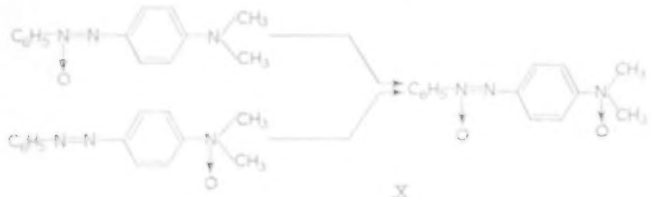


FIG. 4.

spectra of amino-azobenzenes in weakly acidic solution, however, is not readily resolved. It has been seen, from the resonance structure (VIII), that the effect of conjugation between the amino group and the azo group is to increase the basicity of the latter at the expense of the basicity of the former. The deep red colour and the strong spectroscopic absorption of the acidic solutions can be explained by the existence of two tautomeric forms, ammonium and azonium, present in equilibrium, as maintained by cited authors.

Another feature apparently inconsistent with results is the structure assigned by Angeli[14] to the bis-oxidation product of *p*-dimethylamino-azobenzene. By oxidation of Butter Yellow by excess peracetic acid an amino-oxide azoxy is obtained to which Angeli assigned the structure (IX). Among the possible mono-oxidation products, an amino-oxide *β*-azoxy can be obtained only through the *β*-azoxy (VI), which by oxidation can give only the corresponding amino oxide (IX). As the mono-oxidation

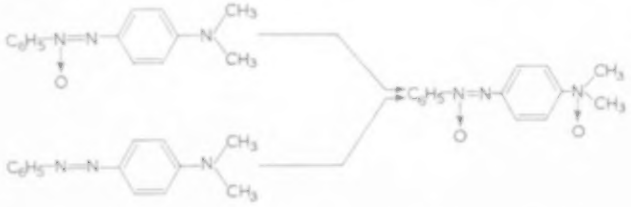
IX



X

furnishes the N-oxide at the amino group, (VII), that is the primary oxidation step, even in the bis-oxidation, and through it, by further oxidation, one can obtain only the amino oxide *α*-azoxy (X). Indeed, of the two azo nitrogen atoms in the azo amino oxide (VII), the *β* nitrogen becomes positively charged, owing to the —I effect of the substituent, and will have less tendency to bind the oxygen atom, which takes up the free electron pair on the *α* nitrogen atom.

To explain this the *p*-dimethylamino-azoxy compounds described by Anderson have been prepared. Additional evidence that the structures assigned to the azoxy isomers are correct was obtained by the action of bromine. The *β* isomer undergoes smooth bromination while the *α* isomer under the same conditions does not react. By oxidation of the *α* isomer with peracetic acid a product was obtained which was



identical with the amino oxide azoxy prepared from Butter Yellow by oxidation with an excess of peracetic acid.

By oxidation of the *β* azoxy (VI) a bis-N-oxide was obtained, having properties different from those of the bis-oxidation product of Butter Yellow. The assigned

[14] A. Angeli, *Rend. Accad. Lincei* **24**, 1190 (1915); *Gazz. Chim. Ital.* **46**, 94 (1916).

structure of amino oxide β azoxy (IX) is therefore correct. The absorption spectra (Fig. 5) are very similar for the two bis-N-oxides, owing to the analogous structures and the lack of different conjugation forms.

Hence, in 4-dimethylamino-azobenzene the nitrogen atom with higher electron density is the amino nitrogen and for the bis-oxidation compound the structure of α-azoxy amino oxide is correct.

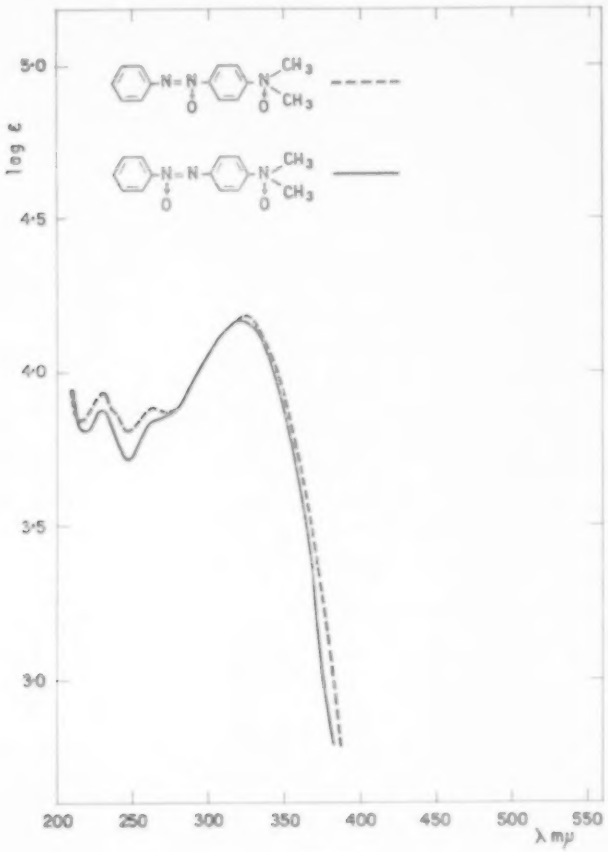


FIG. 5.

EXPERIMENTAL

p-*Dimethylamino-azobenzene amino-oxide* (VII)

To a cold solution of *p*-dimethylamino-azobenzene (10 g, 1 mole) in chloroform (15 ml) a cold solution of perbenzoic acid (6·12 g, 1 mole) was added dropwise. After standing overnight the peracid had disappeared, the solvent was evaporated and the residue stirred for 1 hr with sodium carbonate solution (200 ml) filtered and washed with water. The orange yellow crystals were air dried, washed with ether and dried over P_2O_5 *in vacuo;* yield, m.p. 123–125°, 11 g. Long orange prisms (dioxane), dried for 24 hr *in vacuo* over P_2O_5, yield 9·8 g, m.p. 126–127°. (Found: N, 17·36; Calc. for $C_{14}H_{15}N_3O$: N, 17·42%).

α- and β-p-dimethylamino-azoxybenzenes (V *and* VI)

The isomeric *p*-dimethylamino-azoxybenzenes were prepared by condensation of phenylhydroxylamine with nitroso-dimethylaniline.[11]

The *β* isomer (VI), m.p. 122° (1 g) in chloroform (20 ml) was added to a solution of bromine (1 ml) in chloroform (7 ml); after 4 hr in the refrigerator crystals separated. These were filtered, stirred with sodium carbonate solution, washed with water and dried. Orange yellow plates (ethanol), of brominated azoxy compound, were obtained. (Found: N, 13·20; Calc. for $C_{11}H_{14}BrN_3O$: 13·12%).

The α isomer (V), under the same conditions, was recovered unchanged.

p-*Dimethylamino-α-azoxy-benzene amino oxide* (X)

(a) *bis-Oxidation of the Butter Yellow.* To a fine suspension of *p*-dimethylamino-azobenzene (10 g) in glacial acetic acid (75 ml), 36% hydrogen peroxide (50 ml) was added and the mixture heated at 40° for 48 hr until the purple colour became orange-yellow. To the cooled solution, diluted with an equal volume of water, a great excess (ca. 400 ml) of dilute (1 : 10) H_2SO_4 was added, by cooling in ice. The sulphate of the azoxy-amino-oxide separated as bright orange leaves. After 6 hr in ice the sulphate was filtered, suspended in little water and stirred for 30 min with sodium carbonate solution (200 ml). The crude compound, yellow leaves, (10 g) gave pale yellow prisms (dioxane), m.p. 125–126°, after 3 days over P_2O_5 *in vacuo*. (Found: N, 16·30. Calc. for $C_{11}H_{15}N_3O_2$: N, 16·33%).

(b) *Oxidation of the* p-*dimethylamino-α-azoxy-benzene* (V). To a deep green solution of α-azoxy compound (0·3 g) in glacial acetic acid (10 ml) 36% hydrogen peroxide (1 ml) was added, and heated at 40° for 24 hr. A citron yellow solution resulted which was neutralised with sodium hydroxide and extracted with chloroform. The solvent was evaporated and the residue, washed with benzene and dried *in vacuo* over P_2O_5, melted at 118–123°. The crude compound was poured onto an alumina column in dioxane. The upper broad yellow band gave an yellow product, m.p. 125–126° (dried over P_2O_5 *in vacuo*), identical with the above *p*-dimethylamino-α-azoxybenzene amino oxide, as shown by mixed m.p. and the u.v. spectra. (Found: N, 16·40. Calc. for $C_{11}H_{15}N_3O_2$: N, 16·33%).

(c) *Oxidation of the* p-*dimethylamino-azobenzene amino oxide* (VII). To a suspension of the azocompound amino oxide (2 g) in glacial acetic acid (20 ml), 36% hydrogen peroxide (2 ml) were added and the mixture heated at 40° for 48 hr. The resulting yellow solution was neutralised with sodium hydroxide and extracted with chloroform. The solvent was evaporated to give an yellow residue which was recrystallised from dioxane in pale yellow prisms, m.p. 126–127° (dried for 3 days over P_2O_5 *in vacuo*), identical with the above α-azoxy-amino-oxide compound. (Found: N, 16·51; Calc. for $C_{11}H_{15}N_3O_2$: N, 16·33%).

p-*Dimethylamino-β-azoxybenzene amino oxide* (IX). *Oxidation of the β-azoxy isomer* (VI).

To a solution of *p*-dimethylamino-*β*-azoxybenzene (2 g) in glacial acetic acid (20 ml), 36% hydrogen peroxide (2 ml), were added and the mixture heated at 40° for 24 hr. The resulting orange solution was neutralised with sodium hydroxide and extracted with chloroform. The solvent was evaporated to give brown crystals which were washed with little benzene and recrystallised from dioxane in yellow needles,

m.p. 117–118°, of *p*-dimethylamino-β-azoxy-benzene amino oxide, not identical with the isomer α-azoxy amino oxide, as shown by the physical aspect and m.p. (Found: N, 16·44. Calc. for $C_{14}H_{15}N_3O_2$: N, 16·33%).

Ultra-violet-visible absorption spectra

The absorption spectra were determined in 95% ethanol with a Beckman Model DU Quartz spectrophotometer.

Acknowledgement—The author wishes to thank Bro. Columba Curran, C.S.C., University of Notre Dame, Notre Dame, Ind., U.S.A., for helpful suggestions.

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TOXIC FLUORINE COMPOUNDS CONTAINING THE C–F LINK—X*

RUPTURE OF THE C–F LINK BY ALKALI AND OTHER REAGENTS

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(*Received* 16 *July* 1958)

Abstract—The reactivity of the carbon–fluorine bond in certain ω-fluorocarboxylic acids and esters with respect to nucleophilic attack has been examined. Heating under reflux with 30 per cent sodium hydroxide hydrolyses this type of compound and on this basis a method of fluorine analysis is suggested.

Phenyl magnesium bromide converts methyl fluoroacetate and fluoroacetyl chloride into 1:2:2-triphenylethanol. The so-called unreactive fluorine atom in methyl γ-fluorobutyrate is also removed by this reagent giving 2:2-diphenyltetrahydrofuran.

It has frequently been stated, in general terms, that the carbon and fluorine atoms in fluoroacetates and related compounds are very firmly bound.[1] By comparison with the corresponding chloro-, bromo- and iodo-compounds this is true, nevertheless we have collected a number of instances where the C–F link is easily ruptured, particularly by nucleophilic reagents. Attention is first drawn to the action of sodium hydroxide on fluoroacetates with a view to the development of a simple analytical method for the determination of the fluorine content.

Hitherto recommended methods for breaking down "fluoroacetates" have included:—

(a) Fusion with sodium in an evacuated tube at 400°.[2,3]

(b) Fusion in a stainless steel bomb with sodium peroxide.[3]

(c) For volatile compounds: heating with oxygen at 1250° in a platinum tube and absorbing the resulting hydrofluoric acid in water.[4]

After breakdown by a suitable method, the subsequent determination of fluoride can be carried out by any standard method, e.g. precipitation as lead chlorofluoride[3] or titration with thorium nitrate.

When methyl fluoroacetate or fluoracetic acid is heated under reflux with 10 per cent aqueous sodium hydroxide solution for one hour no fluoride ion is produced. Rather surprisingly little serious attention has been paid to the action of boiling concentrated (e.g. 30 per cent) aqueous alkali on the stability of the C–F link in these compounds. We have therefore investigated the reaction in detail by heating the fluoro compound under reflux with a large excess of 30 per cent sodium hydroxide solution for 1 hr. The free fluoride was then determined by precipitation as lead chlorofluoride followed by a Volhard volumetric estimation.[3] Almost the whole of the fluorine was removed under these conditions. In some instances the fluorine was eliminated within 15 min.

* Part IX, *J. Chem. Soc.* 1929 (1953).

[1] B. C. Saunders, *Phosphorus and Fluorine* p. 115. Cambridge University Press (1957).
[2] P. J. Elvin and W. B. Ligett, *Industr. Engng. Chem.* (*Anal.*) **14,** 449 (1942).
[3] N. B. Chapman, R. Heap and B. C. Saunders, *Analyst* **73,** 434 (1948).
[4] O. I. Milner, *Industr. Engng. Chem.* (*Anal.*) **22,** 315 (1950).

After heating for 1 hr the results with fluoroacetamide were as follows:—

% F in various analyses	Av. % F and deviation	Calc. for $CH_2F{\cdot}CONH_2$
24·51, 24·22, 24·42. 24·28, 24·43, 24·35. 24·34, 23·97, 24·72. 24·93.	24·42 ± 0·24	24·68%

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Fluoroacetamide can be obtained in a highly purified condition[3] and good analyses were obtained. With methyl fluoroacetate, 2-fluoroethanol, 3-fluoropropanol, β-fluoropropionic acid, and benzyl fluoroacetate the results tended to be low (about 1 per cent below the calculated value). The reason for this is at present being investigated. So far, however, it can be readily seen that boiling 30 per cent sodium hydroxide solution is capable of removing virtually the whole of the fluorine. Furthermore these preliminary experiments show that this reaction could form the basis of a rapid analytical method which moreover is safe with toxic and volatile materials. The indications at present are that the large excess of ions may to some extent interfere with the delicacy of the lead chlorofluoride method. Hence although excess of 30 per cent sodium hydroxide solution seems to remove all the fluoride, it may be better to use it in conjunction with some other method, e.g. distillation as hydrofluorosilicic acid and determination of fluoride in the distillate with thorium nitrate. This is at present being examined.*

Trifluoroacetic acid when heated under reflux for 1 hr with 30 per cent sodium hydroxide solution gave no fluoride ion.

Hoffmann[6] made observations on the reactivity of the halogen atoms in a series of 1-bromo-and 1-chloro-ω-fluoroalkanes using N-sodium ethoxide in alcohol and N-potassium hydroxide in 70 per cent alcohol. He made conclusions about the behaviour of the C–F link when not influenced by neighbouring groups. In general there was great resistance to nucleophilic attack, the highest percentage of fluorine hydrolysed was 11 per cent compared with 82 per cent of bromine and 52 per cent of chlorine in a wide range of experiments under standard conditions. Also, as the fluorine atom becomes further separated from the other halogen atom in the molecule, so resistance to hydrolysis increases. The presence of the C–F bond increases the strength of the C–Cl and C–Br bonds in the 1-halo-2-fluoroethanes.

It is evident from the above that any reaction at the C–F link would have to be carried out with some strong nucleophilic reagent to have any chance of success. The obvious choice was the Grignard reagent. It is known that phenyl magnesium bromide converts methyl chloroacetate into 1:1-diphenyl-2-chloroethanol in small yield together with traces of diphenyl.[7] We have shown that when methyl fluoroacetate reacted

* Work being carried out at present (D. L. E. Bronnert and B. C. Saunders) indicates that some F^- is probably retained on the walls of the flask in which the hydrolysis is carried out. This accounts for the low results often obtained. Using 1/20 of the above quantities (cf. Belcher and Macdonald[3]) the results tended to be rather erratic. Further work is necessary to establish the range of applicability of the method.

[3] R. Belcher and A. M. G. Macdonald, *Mikrochim. Acta* 510 (1957).
[6] F. W. Hoffmann, *J. Org. Chem.* XIV, 105 (1949).
[7] Shigeki Horije, *Mem. Inst. Sci. Ind. Res. Osaki Univ.* 7, 143 (1950).

under reflux, without cooling, with 3 moles of phenyl magnesium bromide, 1:2:2-triphenylethanol* was produced. This facile rupture of the C–F link was unexpected and separate experiments showed that at least 77·5 per cent of the fluorine was eliminated as fluoride ion. When the reaction was carried out at 0°, 1:1-diphenyl-2-fluoroethanol was obtained. Three moles of phenyl magnesium bromide reacted with 1 mole of fluoroacetyl chloride, without cooling, to give 1:2:2-triphenylethanol.

Saunders *et al.*[9] demonstrated the difference in reactivity of the fluorine and bromine atoms in 1-fluoro-2-bromoethane. For instance the latter reacted with potassium thiocyanate to give 2-fluoroethyl thiocyanate in 78 per cent yield. We have now shown, however, that ethanolic potassium cyanide will remove both the halogen atoms from 1-fluoro-2-bromoethane giving ethylene dicyanide in 50 per cent yield.

Since alcoholic potassium cyanide solution does not convert methyl fluoroacetate to methyl cyanoacetate (but yields only potassium fluoroacetate) and in view of Hoffmann's experiments cited above, the following mechanism is suggested for the action of potassium cyanide on 1-fluoro-2-bromoethane:

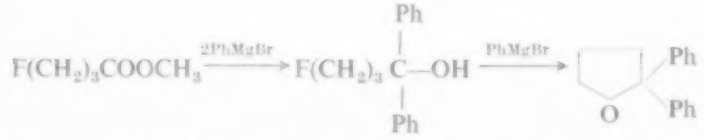
$$CH_2F{\cdot}CH_2Br \xrightarrow{KCN} CH_2F{\cdot}CH_2CN \xrightarrow{-HF} CH_2{=}CH{\cdot}CN \xrightarrow{HCN} CH_2CN{\cdot}CH_2CN$$

This emphasises the fact that the C–F bond is weakened when the carbon is β to a positive carbon atom.

The ease with which the β-fluorine atom can be lost is demonstrated by the difficulty in preparing β-fluoropropionic acid by any kind of substitution reaction. We have also shown that whereas boiling 10 per cent sodium hydroxide solution did not remove any fluorine from methyl fluoroacetate in 1 hr it removed all the fluorine from β-fluoropropionic acid under the same conditions. Even on allowing β-fluoropropionic acid to stand at room temperature for 24 hr with 10 per cent aqueous sodium hydroxide, removal of 94·6 per cent of the fluorine took place

It was considered that, in the next homologue, γ-fluorobutyric acid, the fluorine was too far removed from the carboxyl group to undergo facile elimination as hydrogen fluoride.

Methyl γ-fluorobutyrate was allowed to react with 3 equivalents of phenyl magnesium bromide in the cold followed by heating under reflux. A crystalline solid, m.p. 65–66° was obtained. The compound was fluorine-free, did not contain a hydroxyl group and showed no signs of unsaturation. Infra-red spectra proved the absence of a hydroxyl group, but showed a strong band at 1050 cm^{-1} in agreement with the C—O—C stretching frequency found in tetrahydrofuran and related compounds. Moreover the analysis and reactions agreed with that of 2:2-diphenyltetrahydrofuran and the following pathway for the reaction is suggested:



* One might expect that 1:1:2-triphenylethanol would be formed, but this is not so. A mixed m.p. showed that our product (1:2:2-triphenylethanol) and the compound obtained by reducing 1-bromo-1:1-diphenylacetophenone were identical (cf. Boyle *et al.*[8]).

[8] J. S. W. Boyle, A. McKenzie and W. Mitchell, *Ber. Dtsch. Chem. Ges.* **70,** 2156 (1937).
[9] B. C. Saunders, G. J. Stacey and I. G. E. Wilding, *J. Chem. Soc.* 773 (1949).

Under the same conditions phenyl magnesium bromide and methyl γ-chlorobutyrate failed to produce the diphenyltetrahydrofuran.

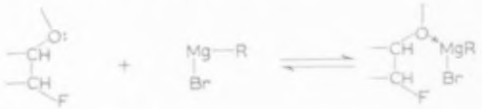
In the course of our systematic investigations of toxic organo-fluorine compounds,[10] we attempted to degrade ethyl β-2-fluoroethoxypropionate by the Barbier–Wieland reaction as follows:

$$R{\cdot}CH_2CH_2COOC_2H_5 \xrightarrow{PhMgBr} R{\cdot}\bar{C}H_2CH_2C(Ph)_2OH \xrightarrow{-H_2O}$$
$$R{\cdot}CH_2CH{=}CPh_2 \xrightarrow{oxid.} R{\cdot}CH_2COOH \quad [R{=}FCH_2CH_2O]$$

The first product actually obtained was diphenyl-2:2′-bromoethoxyethyl carbinol as a result of halogen interchange. This appeared to be the first recorded example of the exchange of fluorine by bromine. Later Hoffmann found that the reaction of aliphatic-bound fluorine with a Grignard reagent could be summarised as follows:

$$R{-}F + PhMgBr \rightarrow PhMgF + R{-}Br \rightarrow Ph{\cdot}R + MgBrF$$

In view of this, it is difficult to state categorically whether the ether linkage β to the C–F bond has a specific influence on the halogen interchange. Doubtless, the fact that the Grignard reagent can co-ordinate with the ether linkage, thus bringing the halogen into close proximity, helps the reaction.



In any case it was of interest to determine whether the lower homologue of the series would also undergo the reaction with the same ease. Accordingly ethyl 2-fluoroethoxy acetate was allowed to react with three equivalents of phenyl magnesium bromide. A fluorine-free compound, m.p. 64–6°, was obtained. Analysis and other evidence, including infra-red spectra, showed it to be diphenyl 2-bromoethoxymethyl carbinol, $BrCH_2CH_2{\cdot}O{\cdot}CH_2C(Ph)_2OH$.

EXPERIMENTAL

Determination of fluorine in a C–F *compound.* An amount of the compound, such as to contain about 200 mg of fluorine was weighed into a 25 ml round-bottomed flask. Pure sodium hydroxide (10 ml, 30 per cent aqueous solution) was added and the mixture heated under reflux for 1 hr. The solution was then made up to 100 ml, and the fluoride ion determined in 25 ml by the lead chlorofluoride method.[3] Results for fluoroacetamide appear on p. 38.

Reaction between phenyl magnesium bromide and methyl fluoroacetate. Bromobenzene (15·7 g) was dissolved in dry ether (50 ml) and half of the solution added to magnesium turnings (2·5 g). After the initial reaction had subsided, the remainder of the bromobenzene was added slowly and the mixture heated under reflux for 15 min, then cooled in ice-water, and a solution of methyl fluoroacetate (3·2 g) in dry ether (15 ml) added with stirring. A vigorous action ensued and a white solid separated which was soon replaced by a heavy oil. The mixture was heated under reflux for 15 min, poured on to a mixture of ice (100 g) and 10 per cent sulphuric acid (60 ml) and

[10] F. J. Buckle and B. C. Saunders, *J. Chem. Soc.* 2774 (1949).

then steam-distilled. On cooling overnight at 0°, the oil which had distilled over solidified (0·514 g) and was readily sublimed at 40°/0·5 mm and recrystallised from ethanol, m.p. 68–9°. Mixed m.p. with authentic diphenyl, 69–70°.

The yellow oil left in the flask after steam distillation was extracted with ether and dried (Na_2SO_4). The aqueous layer contained fluoride (see below), the ethereal layer was fluorine-free. The ethereal layer was evaporated and a viscous oil (6·24 g) remained. On warming the oil with light petroleum (b.p. 40°–60°) and then cooling to 0°, yellow waxy crystals (1·5 g) separated. These were recrystallised from light petroleum (b.p. 40°–60°) and had m.p. 86°. (Found: C, 87·6; H, 6·7. Calc. for $C_{20}H_{18}O$: C, 87·6; H, 6·6 per cent). Mixed m.p. with authentic 1:2:2-triphenylethanol (m.p. 87°) gave no depression.

The product (100 mg) was heated under reflux for 30 min with acetic anhydride (2 ml) and poured into water. The oil which separated solidified and was recrystallised from benzene-light petroleum (b.p. 60–80°) mixture. The 1:2:2-*triphenylethylacetate* thus obtained had m.p. 158° and could be sublimed. (Found: C, 83·7; H, 6·2. $C_{22}H_{20}O_2$ requires C, 83·5; H, 6·4 per cent).

Analysis of the aqueous solution for fluoride ion. Methyl fluoroacetate (2·57 g) was allowed to react with phenyl magnesium bromide as above. The product was not steam distilled, but extracted with ether. The aqueous solution was made up to 500 ml. This solution (25 ml) and concentrated sulphuric acid (25 ml) were mixed and steam distilled in the presence of powdered glass. Fluoride was determined in the filtrate by titration with thorium nitrate.[11] (Found: F^- in 500 ml = 0·41 g. Total fluorine in methyl fluoroacetate = 0·53 g therefore the amount of fluorine converted to F^- by Grignard reaction = 77·5 per cent).

Reaction between phenyl magnesium bromide and methyl fluoroacetate at 0°. The Grignard reagent [bromobenzene (15·7 g), magnesium (2·5 g), ether (50 ml)] was placed in a freezing mixture and methyl fluoroacetate (3·2 g) added dropwise with vigorous stirring so that the temperature did not rise above 0°. The product was acidified, and on standing overnight a yellow oil and white crystals were obtained. The latter (1:1-diphenyl-2-fluoroethanol) were recrystallised from carbon tetrachloride and then from light petroleum (b.p. 60–80°). Yield 2·8 g m.p. 71–2°. (Found: C, 77·2; H, 5·8. Calc. for $C_{14}H_{13}OF$: C, 77·8; H, 6·0 per cent).

Reaction between phenyl magnesium bromide and fluoroacetyl chloride. To the Grignard reagent from bromobenzene (47·1 g), cooled to 0°, fluoroacetyl chloride (9·65 g) in ether (100 ml) was added with stirring. A vigorous reaction followed and an orange-coloured oil separated. The mixture was then heated under reflux for 15 min, poured onto ice (180 g) and dilute sulphuric acid (180 ml) and the ether layer separated, dried (Na_2SO_4) and distilled. A red oil (19·2 g) remained. (The aqueous layer gave a positive test for fluoride ion.) On stirring the oil with light petroleum, crystallisation slowly took place and the solid was recrystallised from ethanol and had m.p. 145–151° (1 g). This was sublimed at 120°/0·2 mm giving a residual solid, m.p. 120° and a liquid sublimate which ultimately crystallised and was recrystallised from light petroleum (b.p. 40–60°). M.p. and mixed m.p. with authentic 1:2:2-triphenylethanol, 85°.

Action of potassium cyanide on bromofluoroethane. Bromofluoroethane (50 g), potassium cyanide (26 g), ethanol (90 ml) and water (15 ml) were heated under reflux

[11] B. C. Saunders, *Phosphorus and Fluorine* p. 115. Cambridge University Press (1957).

for 6 hr. The mixture was cooled, allowed to stand for 2 hr. Solid was filtered off and ethanol removed from the filtrate and the residue fractionated:

(1) B.p. below 20°/21 mm (7·23 g). F(−). CN(−).

(2) B.p. 25°/21 mm (2·5 g). F(+). CN(−).

(3) B.p. 116–120°/2 mm, with charring. (8·0 g of solid). F(−). CN(+). Sublimed readily giving crystals m.p. 53–54°. (Found: N, 34·9. Calc. for $C_2H_4N_2$: N, 35·0 per cent). Mixed m.p. with authentic succinonitrile showed no depression.

Action of potassium cyanide on methyl fluoroacetate. Methyl fluoroacetate (27·6 g), potassium cyanide (18·3 g), methanol (90 ml) and water (5 ml) were heated under reflux for 1 hr, and the mixture filtered. The methanol was slowly distilled off until crystals began to separate. These were dissolved in water giving a cloudy solution which was centrifuged, purified with charcoal and concentrated. The potassium fluoroacetate that separated was recrystallised from ethanol. (Found: C, 20·9; H, 1·8. Calc. for $C_2H_2O_2FK$: C, 20·7; H, 1·7 per cent).

Action of phenyl magnesium bromide on methyl γ-fluorobutyrate. The Grignard reagent [bromobenzene (16·5 g), magnesium (2·6 g) and ether (50 ml)] was cooled to 0° and methyl γ-fluorobutyrate[12] (4·2 g) in ether (10 ml) was added with stirring, and then heated under reflux for 15 min. The mixture was cooled and acidified with dilute sulphuric acid. The ether layer was separated, and the aqueous layer extracted with ether (2 × 10 ml). The ether layers were washed with sodium bicarbonate solution, water and dried ($MgSO_4$). After distilling off the ether, the residue (8·6 g) was distilled.

Two fractions were obtained:

(1) B.p. 80°/0·9 mm and was diphenyl m.p. 67·5°.

(2) B.p. 110–130°/0·9 mm and solidified (2·3 g). This was fluorine-free and recrystallised from ethanol as needles, m.p. 65·5°. The 2:2-*diphenyltetrahydrofuran* thus obtained had mixed m.p. 40–45° with diphenyl. (Found: C, 85·95; H, 7·3. $C_{16}H_{10}O$ requires C, 85·7; H, 7·1 per cent).

Action of phenyl magnesium bromide on ethyl 2-fluoroethoxyacetate. Ethyl 2-fluoroethoxyacetate[10] (5 g) in dry ether (15 ml) was added slowly to the Grignard reagent [from magnesium (2·4 g) and bromobenzene (15·7 g)]. The mixture was boiled under reflux for 25 min, cooled, poured on to ice (100 g) and dilute sulphuric acid (80 ml), and steam-distilled. Diphenyl (0·5 g) came over.

The aqueous residue was extracted with ether, dried ($MgSO_4$) and the ether distilled off and the product recrystallised from ethanol and then from light petroleum (b.p. 40–60°). The *diphenyl 2-bromoethoxymethyl carbinol* thus obtained had m.p. 64–6°. (Found: C, 59·5; H, 5·1. $C_{12}H_{17}OBr$ requires C, 59·8; H, 5·3 per cent).

One of us (P. M-S.) acknowledges with thanks a D.S.I.R. maintenance grant.

[12] Private communication from (the late) M. S. Kharasch.

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ABSOLUTE CONFIGURATION OF α-METHYL-β-ALANINE

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(*Received* 21 *July* 1958)

Abstract—(−)-α-Methyl-β-alanine was correlated through the reaction stages (I–III) with (−)-2-methylbutanol. The resulting absolute configuration is represented by the projection formula (V).

(−)-α-METHYL-β-ALANINE was isolated from human urine in 1951.[1] The excretion of this amino acid by individual cancer patients is reported to vary noticeably and to be related to the neoplastic process.[2] The formation of this compound occurs in the metabolism of dihydrothymine.[3,4] α-Methyl-β-alanine has also been identified as an end-product of valine metabolism.[5,6] Considering the biological importance of this metabolite it is of interest to establish its absolute configuration.

The correlation of the configuration of (−)-α-methyl-β-alanine and (−)-2-methylbutanol was outlined in a preliminary communication[7] and was effected by the conversion of the former compound into optically active 2-methyl-1-phthalimidobutane, earlier obtained from (−)-2-methylbutanol via (+)-1-bromo-2-methylbutane and its reaction with potassium phthalimide.[8]

(±)-α-Methyl-β-phthalimidopropionic acid (Ia) obtained from (±)-α-methyl-β-alanine has now been resolved by fractional crystallisation of the brucine salt into the (+) and (−)-α-methyl-β-phthalimido-propionic acids, showing $[\alpha]_D$ +23° and $[\alpha_D]$ −23° respectively. Hydrolysis of the (−)-antipode with hydriodic and glacial acetic acids gives (−)-α-methyl-β-alanine showing $[\alpha]_D$ −14° (in water) and the melting point 173–175°. The melting point of (±)-α-methyl-β-alanine is 181–182°;[9] the (−)-antipode isolated from urine has the melting point 183–184°, but the optical rotation values have not been reported.[1]

(−)-α-Methyl-β-phthalimidopropionic acid was converted into α-methyl-β-phthalimidopropionyl chloride and (−)-1-diazo-3-methyl-4-phthalimidobutan-2-one (Ib) showing $[\alpha]_D$ −72° (in ethyl acetate). This diazoketone racemises very readily: complete racemisation occurring after short heating in organic solvents or even after standing in the solid state at room temperature. Its conversion to the corresponding methyl ketone must, therefore, be effected immediately after preparation. The resulting (+)-2-methyl-1-phthalimidobutan-3-one (Ic), showing $[\alpha]_D$ +10° (in dichloromethane is also very sensitive with regard to racemisation, and considerable experimental work was performed before (II), required for the present correlation,

[1] H. R. Crumpler, C. E. Dent, H. Harris and R. G. Westall, *Nature, Lond.* **167**, 307 (1951).
[2] K. Fink, R. B. Henderson and R. M. Fink, *Proc. Soc. Exp. Biol. Med.* **78**, 135 (1951).
[3] R. M. Fink, K. Fink and R. B. Henderson, *J. Biol. Chem.* **201**, 349 (1953).
[4] K. Fink, R. E. Cline, R. B. Henderson and R. M. Fink, *J. Biol. Chem.* **221**, 425 (1956).
[5] M. J. Coon, *Fed. Proc.* **14**, 762 (1955).
[6] F. P. Kupiecki and M. J. Coon, *J. Biol. Chem.* **229**, 755 (1957).
[7] K. Balenović and N. Bregant, *Chem. & Ind.* 1273 (1957).
[8] W. Marckwald, *Ber. Dtsch. Chem. Ges.* **37**, 1038 (1904).
[9] M. A. Pollack, *J. Amer. Chem. Soc.* **65**, 1335 (1943).

could be prepared. This showing $[\alpha]_D$ +14° (in benzene) was desulphurised by heating under reflux with Raney nickel catalyst in acetone solution. The resulting (+)-2-methyl-1-phthalimidobutane (III) showing $[\alpha]_D$ +24° has the identical sign of optical rotation as the same compound obtained earlier[8] from (−)-2-methylbutanol. It is known[10] that natural (−)-2-methylbutanol ("active amyl alcohol") has the configuration (IV). The same configuration (IV) can be assigned, therefore, to (+)-2-methyl-1-phthalimidobutane (III) and, consequently, (−)-α-methyl-β-alanine should have the configuration (V). In the earlier proposed terms[11] (−)-α-methyl-β-alanine would, therefore, be (*R*)-α-methyl-β-alanine.

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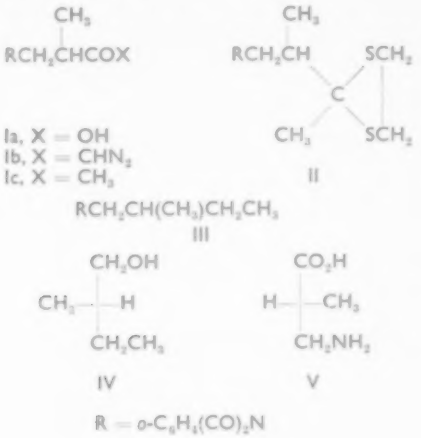

EXPERIMENTAL

(±)-α-*Methyl-β-phthalimidopropionic acid* (Ia). A finely powdered mixture of (±)-α-methyl-β-alanine (prepared from glycine,[12] 7 g, 0·067 mole) and phthalic anhydride (11 g, 0·074 mole) was heated at 110° (temperature of the reaction mixture) in an oil bath for 1 hr. The cooled reaction mixture was recrystallised from ethanol–water (1 : 3). Lustrous leaflets of (±)-α-methyl-β-phthalimidopropionic acid were obtained (13 g, 83%). The analytical sample was recrystallised from the same solvent mixture and dried at 60°/0·01 mm, m.p. 161°. (Found: C, 61·83; H, 4·76. Calc. for $C_{12}H_{11}O_4N$: C, 61·80; H, 4·76%).

Resolution of α-methyl-β-phthalimidopropionic acid. A solution of (±)-α-methyl-β-phthalimidopropionic acid (Ia, 23·3 g, 0·1 mole) in 96% ethanol (400 cc) was added to a solution of brucine (46·6 g, 0·1 mole) in 96% ethanol (250 cc). The ethanol was removed under reduced pressure, and the yellow brucine salt of α-methyl-β-phthalimidopropionic acid was obtained, which crystallised on standing, yield 67 g, and showed $[\alpha]_D^{18}$ −26·6° (*c*, 1·96 in chloroform).

The crude brucine salt (67 g) was dissolved in warm ethyl acetate (1600 cc), filtered, petroleum ether added (b.p. 40–60°, 260 cc) and the solution left at 0° overnight. Yellow crystals separated (51 g) showing $[\alpha]_D^{18}$ − 28·4° (*c*, 1·5 in chloroform). Repeated recry tallisation of this salt from ethyl acetate-petroleum ether afforded the

[10] J. A. Mills and W. Klyne, *Progress in Stereochemistry* (Edited by W. Klyne) p. 188. Butterworths, London (1954); L. Crombie and S. H. Harper, *J. Chem. Soc.* 2685 (1950).
[11] R. S. Cahn, C. K. Ingold and V. Prelog, *Experientia* **12**, 81 (1956).
[12] K. Balenović, I. Jambrešić and I. Ranogajec, *Croat. Chem. Acta* **29**, 87 (1957).

brucine salt of low solubility, $[\alpha]_D$ −44·2° (Found: C, 66·68; H, 6·03. Calc. for $C_{35}H_{37}O_8N_3$: C, 66·97; H, 5·94%).

A more soluble diastereomer could be isolated from the filtrates by fractional crystallisation.

(−)-α-*Methyl-β-phthalimidopropionic acid.* To a suspension of the brucine salt (11·4 g, $[\alpha]_D$ −44°) in water (500 cc) 4 N HCl (250 cc) was added and complete solution occurred; after standing for 1 hr at room temperature, crystals of (−)-α-methyl-β-phthalimidopropionic acid were filtered off, thoroughly washed with water, and dried, yield 3·5 g (83%), $[\alpha]_D^{16}$ −11·3° (*c*, 1·85 in chloroform). The filtrate was extracted with benzene (3 × 100 cc) and after removing the solvent under reduced pressure 0·46 g of (−)-α-methyl-β-phthalimidopropionic acid was obtained (total yield 92%), $[\alpha]_D^{15}$ −24°.

Fractional crystallisation of the acid (3·5 g, $[\alpha]_D$ −11°) from aqueous ethanol (1 : 1) was carried out; 0·9 g of racemic acid was isolated. The optically pure (−)-α-methyl-β-phthalimidopropionic acid was obtained from the filtrates (0·9 g). A small sample showing $[\alpha]_D^{18}$ −20·1° was sublimed for analysis at 110–115°/0·001 mm and showed $[\alpha]_D^{17}$ −24·4° (*c*, 0·98 in chloroform) and the m.p. 145–146° (Found: C, 62·02; H, 4·99. Calc. for $C_{12}H_{11}O_4N$: C, 61·80; H, 4·76%.

(−)-α-*Methyl-β-alanine.* A solution of (−)-α-methyl-β-phthalimidopropionic acid (0·93 g, 0·004 mole) in glacial acetic acid (16 cc) and 47% HI (4 cc) was refluxed 8 hr; the glacial acetic and hydriodic acids were removed under reduced pressure. Water was added to the residue, the separated phthalic acid filtered off, washed with water, and the filtrate extracted with ether. The aqueous layer was evaporated to dryness. Addition of water and evaporation was repeated till no trace of free hydriodic acid remained.

The pale yellow (−)-α-methyl-β-alanine hydriodide was dissolved in water (400 cc) and passed through a column containing IR-4B Amberlite ion-exchange resin (10 g, 21 cc). The filtrate (1000 cc) was evaporated to dryness under reduced pressure, dissolved in water, and filtered (with a small quantity of charcoal). After evaporating the water, crystals of (−)-α-methyl-β-alanine were obtained (0·4 g, 99%), m.p. 169–174° the $[\alpha]_D^{16}$ −9·4° (*c*, 1·37 in water). Sublimation at 110°/0·001 mm gave the pure acid with the m.p. 173–175° and $[\alpha]_D^{17}$ −14·2° (*c*, 0·42 in water) (Found: C, 46·63; H, 8·44. Calc. for $C_4H_9O_2N$: C, 46·59; H, 8·80%).

(−)-1-*Diazo-3-methyl-4-phthalimidobutan-2-one* (Ib). (−)-α-Methyl-β-phthalimidopropionic acid (Ia, 1·09 g, 0·0046 mole, $[\alpha]_D$ −18°) and thionyl chloride (8·5 cc) were refluxed for 1·5 hr (oil bath, 70°). The excess of thionyl chloride was evaporated under reduced pressure, and last traces removed by dissolving the residue in benzene, and evaporating to dryness, leaving crystalline α-methyl-β-phthalimidopropionyl chloride (1·06 g, 96%).

A solution of the foregoing chloride (1·06 g, 0·0042 mole) in benzene (6 cc) was added to an ethereal solution of diazomethane (prepared from 17 g of nitrosomethylurea) at 0°. After standing for 6 hr at 0° the ethereal solution was filtered and evaporated to dryness under reduced pressure. The yield of crude (−)-1-diazo-3-methyl-4-phthalimidobutan-2-one was 1·1 g, (100%), crystallised in yellow needles m.p. 113–114° and $[\alpha]_D^{24}$ −70° (*c*, 2·345 in ethyl acetate). The analytical sample was recrystallised from ethyl acetate–petroleum ether, m.p. 119° (decomp.) (Found: C, 60·96; H, 4·49. Calc. for $C_{13}H_{11}O_3N_3$: C, 60·69; H, 4·31%).

After heating this diazoketone in organic solvents or after prolonged standing at room temperature racemisation occurred.

(+)-2-*Methyl*-1-*phthalimidobutan*-3-*one* (Ic). To a solution of 1-diazo-3-methyl-4-phthalimidobutan-2-one (Ib, 0·32 g, 0·0012 mole) in chloroform (3·5 cc) at 0°, 47% HI (1·5 cc) was added with stirring. After standing for 15 min at −5° the reaction mixture was diluted with cold water (5 cc) and cold chloroform (3 cc). To the separated chloroform layer cold water (10 cc) and mercury (1 cc) were added, and the mixture shaken until the chloroform layer became colourless. The chloroform solution was treated with a small quantity of charcoal, filtered, and evaporated to dryness under reduced pressure. The crystalline residue of (+)-2-methyl-1-phthalimidobutan-3-one (0·28 g, 100%) showed $[\alpha]_D$ +7·6°; the analytical sample was recrystallised from dichloromethane and sublimed at 70°/0·001 mm. The pure compound crystallised in colourless needles, m.p. 82°, $[\alpha]_D^{24}$ +9·8°. (*c*, 0·61 in dichloromethane). (Found: C, 67·34; H, 5·49. Calc. for $C_{13}H_{13}O_3N$: C, 67·52; H, 5·67%).

(+)-2-*Methyl*-1-*phthalimidobutan*-3-*one ethylene mercaptol* (II). 2-Methyl-1-phthalimidobutan-3-one (Ic, 0·92 g, 0·004 mole) was dissolved at −20° in a mixture of ethanedithiol (14 cc) and ether (14 cc), and a solution of boron trifluoride ether complex (4 cc) in ether (20 cc) added, at −20°. The mixture was kept at −20° for 1 hr and then for 4 days at room temperature. Afterwards the ethereal solution was washed with water and evaporated to dryness. The traces of ethanedithiol were removed by drying at 0·01 mm at room temperature. The crystalline residue of (+)-2-methyl-1-phthalimidobutan-3-one ethylene mercaptol (1·25 g, 100%) showed $[\alpha]_D$ +7°. Recrystallisation from benzene–petroleum ether and sublimation at 120°/0·01 mm gave colourless needles, m.p. 126–128°, $[\alpha]_D^{20}$ +14° (*c*, 0·93 in benzene). (Found: C, 58·69; H, 5·58. Calc. for $C_{15}H_{17}O_2NS_2$: C, 58·60; H, 5·57%).

(+)-2-*Methyl*-1-*phthalimidobutane* (III). A solution of the foregoing mercaptol (II, 0·5 g) in acetone (80 cc) was heated under reflux with Raney nickel catalyst (7 g, W-1 activity) with stirring for 7 hr, and cooled. The catalyst was filtered off and washed with acetone, and the combined acetone filtrates evaporated under reduced pressure. A pale yellow oil remained (0·32 g, 93%, $[\alpha]_D$ −2·5°) which after two distillations at 60°/0·001 mm became colourless and consisted of pure (+)-2-methyl-1-phthalimidobutane, with $[\alpha]_D^{25}$ +24° (*c*, 0·56 in benzene). The $[\alpha]_D$ +7·5° was reported for the same compound obtained from natural, not quite pure (−)-2-methylbutanol.[8] (Found: C, 72·03; H, 6·80. Calc. for $C_{13}H_{15}O_2N$: C, 71·86; H, 6·96%.)

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EXTENSION OF THE BISCHLER–NAPIERALSKI REACTION—II

SYNTHESIS OF PYRROLINE DERIVATIVES

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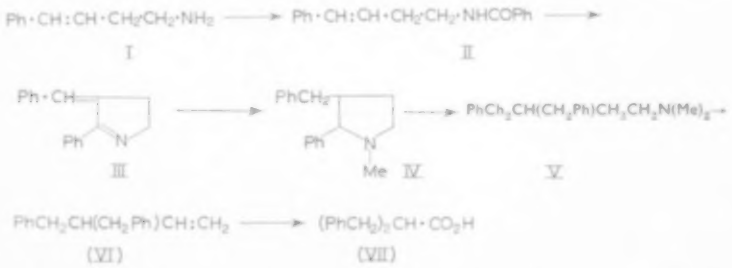
(*Received* 26 *July* 1958)

Abstract—Acyl derivatives of 4-phenyl-but-3-enylamine on treatment with phosphoryl chloride gave good yields of pyrrolines. Pyridine derivatives were not obtained.

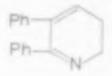
IN Part I[1] the Bischler–Napieralski reaction was applied to the cyclisation of acyl *cyclo*hexa-1:4-dienylamines yielding *iso*quinoline derivatives. The reaction has now been extended to the cyclisation of acyl derivatives of 4-phenyl-but-3-enylamine (I). Thus benz-4-phenyl-but-3-enylamide (II) cyclises to Δ^1-2-phenyl-3-benzal-pyrroline (III) the structure of which was proved by exhaustive methylation. The ultra-violet spectrum showed the presence of a fairly extended conjugated system. The infra-red spectrum showed (at a concentration of 7% in carbon tetrachloride) strong absorption at 3098 and 3048 cm^{-1} due to aromatic C—H stretching vibrations and absorption of equal intensity at 2945 and 2879 cm^{-1} due to aliphatic C—H stretching vibrations. Absorption due to C=C and C=N stretching vibrations was observed at 1636 (*w*) and 1563 cm^{-1} respectively. No absorption was observed in the region corresponding to the N—H stretching vibration. The methiodide of (III) was reduced catalytically to the N-methyl-tetrahydro-base (IV) which was converted through the methiodide to the hydroxide. (IV) was recovered when the latter was subjected to the Hofmann degradation but a modified Emde degradation[2] gave a dihydromethine base (V) the methiodide of which on Hofmann degradation gave 3-benzyl-4-phenyl-but-1-ene (VI), and this on oxidation gave dibenzylacetic acid (VII). Similarly, acet-4-



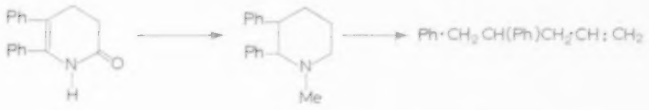
phenyl-but-3-enylamide cyclises to give Δ^1-2-methyl-3-benzal-pyrroline. The structure was proved by a similar degradation process and the final product, β-benzylbutric acid, identified as the anilide.

[1] S. Sugasawa and R. Tachikawa, *Tetrahedron*. In press.
[2] S. Sugasawa and H. Matsuo, *Pharm. Bull. (Japan)* **4**, 142 (1956).

The possibility that cyclisation of (II) might yield 5:6-diphenyl-2:3-dihydropyridine (VIII) was investigated. 5:6-diphenyl-3:4-dihydro-pyrid-2-one (IX)[3] was reduced and methylated to 1-methyl-5:6-diphenylpiperidine (X) and the quaternary iodide of the latter when subjected to Emde and Hofmann degradations gives 4:5-diphenyl-pent-1-ene (XI) which on oxidation yields β:γ-diphenylbutyric acid (XII) (m.p. 93°) identical with an authentic specimen of the acid, and a mixed m.p. with dibenzylacetic acid (m.p. 93°) showed a depression.



VIII



IX X XI

XII

EXPERIMENTAL

2-Phenyl-3-benzalpyrroline (III). 4-Phenyl-3-butenylamine (I) obtained by catalytic reduction of cinnamyl cyanide[4] was benzoylated giving benz-4-phenyl-but-3-enylamide (II). The latter (5 g) was cyclised by refluxing (3 hr) with benzene (30 cc) and phosphoryl chloride (25 cc). The yellow reaction mixture was distilled *in vacuo* to remove benzene and excess phosphoryl chloride, then treated with ice and the acid solution neutralised with potassium carbonate. The oil which separated was extracted with benzene and the basic product extracted from the benzene solution with 3% HCl. The crude base (4·35 g, 93·5%) obtained from the acid solution in the usual way crystallised from hexane as colourless needles, m.p. 110–111°. (Found: C, 87·0; H, 6·5; N, 6·1; $C_{17}H_{15}N$ requires: C, 87·5; H, 6·4; 6·0%). The *picrate* formed yellow needles m.p. 192·5–193·5° from ethanol (Found: C, 59·5; H, 3·7; N, 11·8; $C_{23}H_{18}O_7N_4$ requires: C, 59·7; H, 3·9; N, 12·1%). Infra-red: 1636 cm^{-1} (w. C=C), 1563 cm^{-1} (s. C=N). No absorption in the region of the NH stretching vibration. Ultra-violet: 248 mμ (log $\varepsilon = 4{\cdot}05$), 254 mμ (log $\varepsilon = 4{\cdot}05$), 293 mμ (log $\varepsilon = 4{\cdot}37$). An attempt to dehydrogenate (III) by heating (5 hr) with palladium carbon in *p*-cymene and ethyl cinnamate at 190° gave a scarlet compound m.p. 205° the analysis of which indicated a trimer of dehydrogenated (III). (Found: C, 88·7; H, 5·85; N, 5·4; mol. wt. 694; $(C_{17}H_{13}N)_3$ requires: C, 88·3; H, 5·7; N, 6·1%).

1-Metyl-2-phenyl-3-benzylpyrrolidine (IV). The base (III) when treated with methanolic methyliodide gave a methiodide m.p. 169·5–170·5° (decomp). The latter (4·4 g) converted to the chloride was reduced in ethanol over Adam's platinum until 2 molar equivalents of hydrogen were absorbed yielding (IV, 3·01 g, 85%) m.p. 71°.

[3] A. D. Campbell and I. D. R. Stevens, *J. Chem. Soc.* 959, (1956).
[4] D. Barnard and L. Bakeman, *J. Chem. Soc.* 926 (1950).

(Found: C, 86·05; H, 8·1; N, 5·5; $C_{17}H_{19}N$ requires: C, 86·0; H, 8·4; 5·6%). The *picrate* formed yellow needles m.p. 200·5–201·5° from ethanol. (Found: C, 60·0; H, 4·6; N, 11·3; $C_{24}H_{24}O_7N_4$ requires: C, 60·0; H, 5·0; N, 11·7%). The *methiodide* separated in colourless needles m.p. 192° from methanol-ether. (Found: C, 58·1; H, 6·0; N, 3·45; $C_{19}H_{24}NI$ requires: C, 58·0; H, 6·15; N, 3·6%). 1-*Methyl*-2-*phenyl*-3-*benzalpyrrolidine*. When the hydrogenation of the chloride was stopped after uptake of 1 molar equivalent of hydrogen the dihydro-compound was obtained. This is a low-melting base characterised as its *methiodide* m.p. 226° (decomp) from methanol. (Found: C, 58·2; H, 5·7; N, 3·3; $C_{19}H_{22}NI$ requires C, 58·3; H, 5·7; N, 3·6%).

N:N-*Dimethyl*-3-*benzyl*-4-*phenylbutylamine* (V). The methiodide of (IV) (1·1 g) converted to the corresponding chloride was dissolved in aqueous sodium hydroxide (20 cc, 20%), and Raney nickel alloy (0·5 g) added in portions at 20–25° with stirring (2 hr). The metal was filtered off, the base extracted with benzene, washed with saturated sodium chloride solution, dried and the solvent removed. The residue distilled at 171–175°/3·5 mm to give the pure amine in nearly quantitative yield. The amine reacted exothermically with methyl iodide to form the methiodide which crystallised from methanol-ether in white scales m.p. 165–167°. (Found: C, 58·9; H, 7·0; N, 3·3; $C_{20}H_{28}NI$ requires: C, 58·8; H, 6·9; N, 3·4%). The *picrate* separated in yellow rhombic crystals m.p. 125–125·5° from methanol-ether. (Found: C, 60·6; H, 5·7; N, 11·4; $C_{25}H_{26}O_7N_4$ requires: C, 60·7; H, 5·3; N, 11·3%).

Dibenzylacetic acid. The methiodide (2·87 g) of the amine (V) was converted to the hydroxide which was subjected to crack-distillation *in vacuo* yielding a fraction (b.p. 160°/3 mm) consisting of unchanged amine and a non-basic product. The letter (0·95 g, 64·8%) was freed from the amine by treatment with HCl. The ultra-violet spectrum, 259 mμ (log ε = 2·53), indicated the absence of a double bond conjugating with the phenyl nucleus. The infra-red, observed in a cell (0·15 mm thickness) 1641 cm^{-1} (s. C=C), 994, 910 cm^{-1} (s. C—H out of plane deformation vibration of vinyl group). It is presumed that the non-basic product is 3-benzyl-4-phenyl-but-1-ene (VI). The latter (70 mg) was oxidised in acetone by addition of $KMnO_4$ (140 mg) in acetone (14 cc) at room temp. with stirring. MnO_2 was removed by filtration, washed with water and the washings added to the acetone filtrate. The acetone was removed *in vacuo* and the aqueous solution shaken with benzene, separated and acidified with HCl, when dibenzylacetic acid was deposited as an oil, which solidified and crystallised from *n*-hexane as colourless crystals m.p. 92–93° (Found: C, 80·2 H, 6·4. Calc. for $C_{15}H_{16}O_2$: C, 80·0; H, 6·7%). The acid was identified with an authentic specimen of debenzylacetic acid.

5:6-*Diphenyl*-3:4-*dihydropyrid*-2-*one*[3] (IX). A solution of δ-oxo-γ:δ-diphenylvaleronitrile (20 g) in *tert*.-butanol was refluxed with methanolic potassium hydroxide solution (30%), mixed with *tert*.-butanol (400 cc) for 10 hr during which the pyridone (IX) separated as a solid (13·7 g, 68·4%) and crystallised from ethanol as colourless prisms m.p. 215° (Found: C, 81·85; H, 6·1. Calc. for $C_{17}H_{15}ON$: C, 81·9; H, 6·1%). Infra-red (Nujol) 3220, 3110 cm^{-1}. (N—H), 1665 cm^{-1} (lactam C=O), 1638 cm^{-1} (C=C).

5:6-*Diphenyl-piperid*-2-*one*. The pyridone (IX, 1·6 g) methanol-dioxane (7 : 5) on hydrogenation at 50° over Adams platinum catalyst, absorbed a molar equivalent of hydrogen in 2 hr. The crude product was purified from ethanol (1·15 g, 73%) as

colourless fine needles m.p. 183·5–184·5° (Found: C, 81·0; H, 7·0; N, 5·5. $C_{17}H_{17}ON$ requires: C, 81·2; H, 6·8; N, 5·6%). The band at 1638 cm^{-1} had disappeared.

2:3-*Diphenylpiperidine*. To an ether solution of lithium aluminium hydride (0·1 g) the above piperidone (0·58 g) in dioxane was added and refluxed for 3 hr. Wet ether was added to decompose the adduct and the solvents removed *in vacuo*. The residue a mixture of unchanged piperidone and 2:3-*diphenylpiperidone* was distilled, yielding the pure piperidine which on recrystallisation from ethanol gives colourless prisms m.p. 86·5–87·5° (Found: C, 85·9; H, 8·2; N, 6·0. $C_{17}H_{19}N$ requires C, 86·0; H, 8·1; N, 5·9%). On treatment with formic acid and aqueous form aldehyde the piperidine gave 1-*methyl*-5:6-*diphenylpiperidine* (X) which was purified by distillation b.p. 159–160°/1·5 mm. The *picrate* m.p. 149–150·5° and the *methiodide* colourless cubes m.p. 254° decomp. from ethanol (Found: C, 57·7; H, 6·3; N, 3·5. $C_{19}H_{24}NI$ requires: C, 58·0; H, 6·15; N, 3·6%) were not identical with those of (IV). The methiodide, subjected to the Emde degradation with sodium amalgam (5%) under the usual conditions, gave N:N:4:5 diphenylpentylamine, b.p. 165°/2–2·5 mm (64%). The *picrate* formed yellow scales, m.p. 121–122°, from ether-methanol (Found: C, 60·7; H, 5·7; N, 11·5. $C_{25}H_{26}O_7N_4$ requires: C, 60·7; H, 5·3; N, 11·3%). The methiodide was obtained in quantitative yield as plates m.p. 164–165° from methanol-ether (Found: C, 58·6; H, 6·9; N, 3·7. $C_{20}H_{28}NI$ requires C, 58·7; H, 6·9, N, 3·4%). The methiodide converted to the methohydroxide (0·5 g) submitted to crack-distillation *in vacuo*, gave $\Delta^1$4:5-*diphenylpentene* (XI) b.p. 144–146° (0·16 g, 59) and the latter on oxidation gave β:γ-diphenylbutyric acid (XII), as colourless cubes from hexane m.p. 93° (Found: C, 79·6; H, 6·7. Calc. for $C_{16}H_{16}O_2$: C, 80·0; H, 6·7%). Mixed with dibenzylacetic acid (VII) m.p. 93°, the mixture melted over a range 70–77°. (XII) was found to be identical with a specimen synthesised by condensation of desoxybenzoin with ethyl cyanacetate according to Cope.[5] The synthetic acid crystallised as colourless prisms m.p. 94–95·5° (Found: C, 79·7; H, 6·8. Calc. for $C_{16}H_{16}O_2$; C, 80·0; H, 6·7%). Mixed with (XII) there was no depression. Infra-red spectra of the two acids were also identical over the whole range.

Acet-4-phenyl-but-3-enylamide. Acetylation of 4-penyl-but-3-enylamine (2·42 g) with acetic anhydride (5 cc) on a steam-bath gave the acetyl compound in good yield which crystallised from *n*-hexane in colourless plates m.p. 73–74° (Found: C, 76·1; H, 8·1; N, 7·5; Calc. for $C_{12}H_{15}ON$: C, 76·15; H, 8·0; N, 7·4%). Treatment of the acetyl compound with phosphoryl chloride in boiling benzene gave Δ^1-2-*methyl*-3-*benzalpyrroline* (90%) which crystallised from *n*-hexane in prisms m.p. 61–63°. The *picrate* formed yellow needles m.p. 224° (decomp.) from ethanol. (Found: C, 54·1; H, 4·4; N, 14·3; $C_{18}H_{16}O_4N_4$ requires: C, 54·0; H, 4·0; N, 14·0%). The *methiodide* formed colourless needles m.p. 266·5° (decomp.) from methanol-ether (Found: C, 49·7; H, 5·3; N, 4·8; $C_{13}H_{16}NI$ requires: C, 49·9; H, 5·15; N, 4·5%). Reduction of the methiodide with Adams platinum catalyst absorbed 2 molar equivalents of hydrogen and gave 1:2-*dimethyl*-3-*benzylpyrrolidine* b.p. 109–112°/2·5–3 mm the *methiodide* of which crystallised from methanol-ether in needles m.p. 212–213° (decomp.) (Found: C, 50·6; H, 6·9; N, 4·0; $C_{14}H_{22}NI$ requires: C, 50·8; H, 6·7; N, 4·2%). The methiodide (1·07 g) on treatment with Raney nickel (in the presence of alkali) gave N:N dimethyl 3-benzylpentylamine, (the methiodide of which formed) colourless plates from methanol-ether m.p. 115·5–116·5° (Found: C, 51·8; H, 7·4;

[5] L. Phalnikar and S. K. Nargund, *J. Univ. Bombay*, **3**, 1849 (1939); *Chem. Abstr.* **34**, 2819 (1940).

N, 4·0. $C_{15}H_{26}NI$ requires: C, 51·9; H, 7·55; N, 4·0%). On exhaustive methylation (Hofmann) the methiodide (0·42 g) gave a nitrogen free compound (0·08 g. 41%). The latter (60 mg) oxidised by $KMnO_4$ in acetone gave α-benzylbutyric acid (40 mg) which was converted to the anilide, colourless needles from hexane m.p. 90° (Found: C, 80·3; H, 7·7; N, 5·5; Calc. for $C_{17}H_{19}ON$: C, 80·6; H, 7·6; N, 5·5%). It was identical with an authentic specimen prepared from α-benzylbutyric acid, obtained from benzylethylmalonic acid.

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AN UNUSUAL REARRANGEMENT OF AN ACYL AZIDE*

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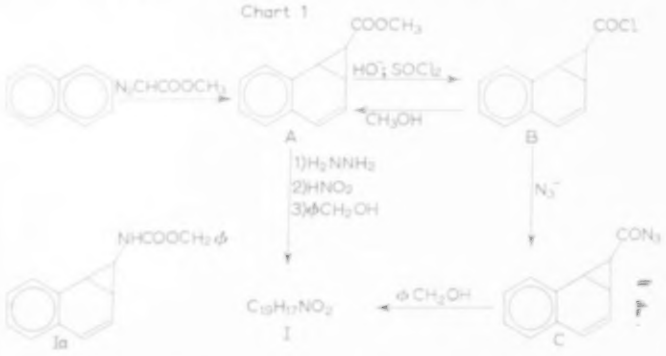
Abstract—Benznorcaradienycarbonyl azide (from naphthalene and methyl diazoacetate by known or unexceptional steps) decomposes on heating with benzyl alcohol in benzene to nitrogen and $C_{19}H_{17}NO_2$ (I). It is clear, from the fact that carbon dioxide is not evolved in the hydroxide-catalyzed cleavage to benzyl alcohol and $C_{12}H_{11}NO_2$ (II), that (I) is not a urethane, but a product of unexpected structure. By degradative and analytical methods and by independent synthesis, we have assigned the structure 2-benzyloxy-6:7-benzo-3-aza*bicyclo* [3.2.2] nona-6:8-diene-4-one to (I) (Chart 2). To our knowledge, no similar rearrangement during a Curtius reaction is recorded.

*cyclo*HEPTATRIENYLIUM or tropylium ion, the parent of the seven-membered aromatic series, was discovered in 1954.[1] Subsequently, it was synthesized by Dewar and Pettit[2] from "ethyl norcaradiene carboxylate" by way of the carbonyl azide and Curtius rearrangement to tropylium *iso*cyanate. Benztropylium ion immediately became one of the next members of the series towards which synthetic efforts were directed. Dewar and Pettit‡ at Queen Mary College and Doering and Hoffmann[3] at Yale independently undertook the synthesis by way of the Curtius rearrangement of benznorcaradiene carbonyl azide (Chart 1, C). Both efforts failed and were abandoned on the announcement of a successful synthesis by the group at the E.T.H. in Zürich.[4]

The failure of the Doering–Hoffmann effort (Chart 1) seemed the more unreasonable since the crucial step had apparently proceeded uneventfully. Naphthalene had

Chart 1



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† National Science Foundation Predoctoral Fellow, 1954–57.

[1] W. von E. Doering and L. H. Knox, *J. Am. Chem. Soc.* **79**, 352 (1957).

[2] M. J. S. Dewar and R. Pettit, *Chem. & Ind.* 199 (1955); *J. Chem. Soc.* 2021, 2026 (1956).

‡ M. J. S. Dewar and R. Pettit, privately communicated.

[3] W. von E. Doering and A. K. Hoffmann, VIII/'54–V/'55 to remain unpublished except for the relevant experiments reported in the experimental section of this paper. Unless explicitly indicated, the experimental details are those elaborated by the present authors.

[4] H. H. Rennhard, E. Heilbronner and A. Eschenmoser, *Chem. & Ind.* 415 (1955); H. H. Rennhard, G. Di Modica, W. Simon, E. Heilbronner and A. Eschenmoser, *Helv. Chim. Acta* **40**, 957 (1957).

been treated with methyl diazoacetate according to Buchner and Hediger[5] to give methyl benzonorcaradiene carboxylate. By the usual sequence—reacting with hydrazine, nitrous acid and heating with benzyl alcohol in benzene—one had expected to obtain the urethane, (Ia), and, indeed, a crystalline product of this formula, $C_{19}H_{17}NO_2$ (I), had been isolated with no great difficulty. The reduction of (I) with lithium aluminum hydride had been followed by quaternization with methyl iodide, but the resulting quaternary salt failed under a variety of conditions to ionize with valence tautomerism to the desired benztropylium cation.

The possibility that the scheme might have gone amiss prior to the Curtius rearrangement was rejected in the following way. The structure of benznorcaradiene carbonyl chloride (Chart 1, B) was soundly related to that of the original ester (Chart 1, A) by the cyclic interconversion shown in Chart 1. Benznorcaradiene carbonyl azide was then prepared from this acid chloride by treating with sodium azide and rearranged by heating with benzyl alcohol in benzene. The product of this alternate reaction sequence was the same as the compound (I) obtained from the hydrazide.

The possibility was considered that the structure of the starting material had been incorrectly assigned. In the parent series, only ethyl "norcaradiene" carboxylate among the several isomeric *cyclo*heptatriene carboxylic acids (Buchner acids) had been converted successfully to tropylium ion by rearrangement of the corresponding azides.[2] In confirmation of the structural assignment, Buchner and Hediger[5] had degraded benznorcaradiene carboxylic acid to 3-(*o*-carboxyphenyl) *cyclo*propane-1:2-dicarboxylic acid and thence to *transcyclo*propane-1; 2; 3-tricarboxylic acid.* Some measure of further support comes from comparison of the ester with benznorcaradiene itself. Synthesized by the photochemical decomposition of diazomethane in naphthalene and purified by conversion to a crystalline dibromide and regeneration with zinc, benznorcaradiene is oxidized to a dicarboxylic acid, $C_{11}H_{10}O_4$, which resists further oxidation by permanganate-periodate and is consistently formulated as 2-(*o*-carboxyphenyl) *cyclo*propane-1-carboxylic acid. The n.m.r. spectrum of benznorcaradiene shows 3·9 aromatic hydrogen atoms at −12 c.p.s., 2·3 olefinic at 24 c.p.s., and a total of 3·8 aliphatic hydrogen atoms, 2·8 at 205 c.p.s. and 1·0 at 279 c.p.s. The presence of two rather than four olefinic atoms is consistent with the benznorcaradiene structure and inconsistent with the isomeric benz*cyclo*heptatriene structure.† The ultraviolet spectra of benznorcaradiene and methyl benznorcaradiene carboxylate (Chart 1, A; Fig. 1) are almost identical and are closely similar to that of 1:2-dihydronaphthalene.‡ It follows that benznorcaradiene and its derivatives have a double bond conjugated with the benzene ring and that Buchner and Hediger very

* The stereochemistry of this acid is established.[8]

† In contrast to the tropilidene series where the question of valence tautomerism is difficultly resolvable, in the benztropilidene series, subtle questions of structure are removed by the overwhelmingly dominant influence of the fused benzene ring. Thus, fusion to the $\alpha:\beta$ and $\gamma:\gamma'$ positions (relative to the CH_2 group of *cyclo*heptatriene) must enforce a *cyclo*heptatriene structure on the seven-membered ring, whereas $\beta:\gamma$ fusion demands a norcaradiene structure. Were the ring structures otherwise the benzene ring would become quinonoid.

‡ The spectrum of the last compound has also been compared to that of ethyl benznorcaradiene carboxylate by Badger and coworkers.[8]

[5] E. Buchner and S. Hediger, *Ber. Dtsch. Chem. Ges.* **36**, 3502 (1903).

[6] H. R. Ing and W. H. Perkin, Jr., *J. Chem. Soc.* **125**, 1814 (1924).

[7] E. J. Corey, H. J. Burke and W. A. Remers, *J. Am. Chem. Soc.* **77**, 4941 (1955); W. von E. Doering, G. Laber, R. Vonderwahl, N. F. Chamberlain and R. B. Williams, *J. Am. Chem. Soc.* **78**, 5448 (1956); M. V. Evans and R. C. Lord, *Abstracts of Papers*, 130*th Meeting*, *Am. Chem. Soc.* Sept. 16–21, 1956, p. 41 R. Atlantic City, N.J.

[8] M. Badger, B. J. Christie, H. J. Rodda and J. M. Prykz, *J. Chem. Soc.* 1179 (1958).

probably assigned the structure of benznorcaradiene carboxylic acid correctly. It seemed at first implausible that (I) might not have the structure (Ia) and that the Curtius rearrangement itself should be the seat of the trouble, in view of the long history of unchallenged reliability lying behind the Curtius rearrangement.[9] Several properties of (I) are, however, in such complete discord with the structural hypothesis (Ia) that one is forced to suspect the rearrangement step.

The ultraviolet spectrum of (I, Fig. 1) is that of a tetralin and not that of a 1:2-dihydronaphthalene. Consequently (I) cannot contain an olefin grouping conjugated with the aromatic ring. Mild treatment of (I) with alkali causes hydrolysis to benzyl alcohol, (C_7H_8O) and a compound (II), $C_{12}H_{11}NO_2$. The presence in (II) of twelve carbon atoms instead of eleven ($C_{11}H_{11}N$ and CO_2) demanded on hydrolysis of a benzyl carbamate of the empirical formula $C_{19}H_{17}NO_2$ (I) is also inconsistent with

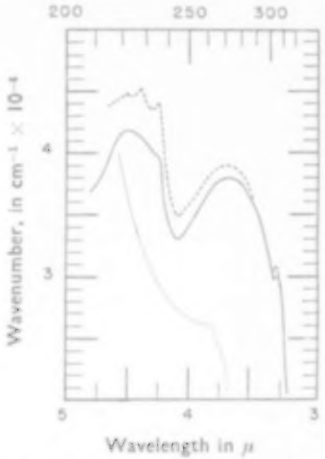


FIG. 1. Ultraviolet spectra of benznorcaradiene (———), methyl benznorcaradiene (– – – – –, Chart 1, A) and compound I (. . . . . , Chart 2).

the formulation (Ia). The thin reservation that (II) may be a carbamic acid of unusual stability cannot be maintained against the observation that simple heating in benzyl alcohol reconverts (II) to (I).

With the removal of (Ia) as the correct structure, it was clear that the Curtius rearrangement had taken an unexpected turn, the pursuit of which was irresistible. As experimental work progressed, it became increasingly evident that the crucial substance in the structural problem was not (I) but (II), the hydrolysis product; and it was mainly to this substance that our attention was directed.

From an intense band at 5·98 μ (1672 cm^{-1}) in the infrared spectrum (experimental section) the presence of a carbonyl group in (II) can be inferred. Catalytic reduction with the absorption of two atoms of hydrogen indicates the presence of a double bond in (I) and (II). Any question that the unsaturation be of some other type is removed by comparing the n.m.r. spectrum of (I) and its equally accessible dihydro derivative. In dioxane solution (I) shows a peak at 38 c.p.s. which is due to olefinic hydrogen; by contrast dihydro-1 has no band in this region.

Consideration of the mechanistically plausible paths of further reaction that might

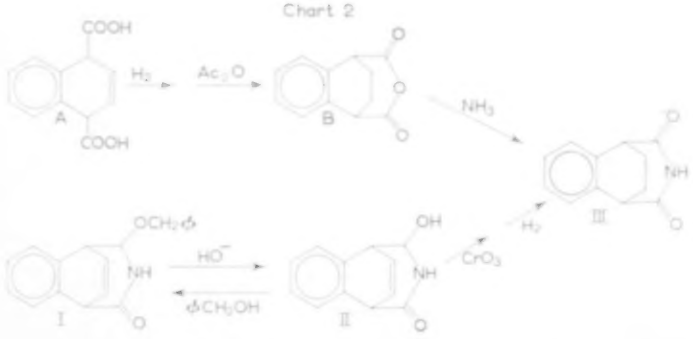
[9] P. A. S. Smith, *Organic Reactions* Vol. III, p. 337. John Wiley and Sons, Inc., New York (1946).

be open to the initially formed *iso*cyanate (Chart 5), coupled with analysis of the facile hydrolysis of (I) to (II) (Chart 3) and the other data above led to a structural hypothesis for (II). The most direct proof of this structure involves a two-step transformation and an independent synthesis.

Oxidation of (II) ($C_{12}H_{11}NO_2$) proceeds smoothly with chromic acid in acetone solution with loss of two hydrogen atoms to $C_{12}H_9NO_2$. This behavior is strongly indicative of the presence of an hydroxyl group in (II). The oxidation product can be hydrogenated catalytically to (III), a dihydro derivative, $C_{12}H_{11}NO_2$, in further confirmation of the presence of an olefinic group in the series. Absorption bands of (III) in the infrared (Experimental Section) at 5·86 (1706) and 5·94 μ (1684 cm^{-1}) indicate the presence of two carbonyl groups.

The independent synthesis of (III) is effected from the known 1:4-dihydronaphthalene-1:4-dicarboxylic acid[10] (Chart 2, A). Hydrogenation of the double bond and heating with acetic anhydride produces 1:2:3:4-tetrahydro-1:4-naphthalenedicarboxylic anhydride (Chart 2, B). In a single step the anhydride is opened with ammonia, presumably to the monoamide, and then closed to 1:2:3:4-tetrahydro-1:4-naphthalenedicarboximide (Chart 2, III) by heating to 300°. The synthesis involves reactions of such a transparent nature that the structure assigned to the end-product (III) hardly requires more elaborate justification. This synthetic material is identical in m.p. and infrared spectrum to (III) obtained from (II) by chromic acid oxidation and catalytic hydrogenation. 2-Hydroxy-6:7-benzo-3-aza*bicyclo* [3.2.2] nona-6:8-dien-4-one follows as the structure of (II) (Chart 2, II), once attention is called to the absence of an aldehydic carbonyl group in the infrared spectrum and the structural impossibility of placing the olefinic linkage at any other position in the skeleton.

Chart 2

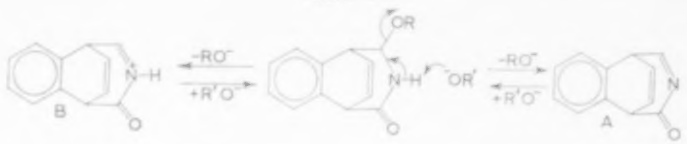


Assignment of a structure to (I) depends almost solely on rationalizing the facile hydrolysis of (I) by dilute alkali to (II) and the equally facile regeneration of (I) from (II) by heating with benzyl alcohol. The absence of any gross structural change in the interconversion is attested to by the close similarity in the infrared and ultraviolet spectra of (I) and (II) and by the presence in each of an olefinic double bond. The replacement of the benzyloxy group is, furthermore, independent of the presence of the double bond, since dihydro-I can be hydrolyzed to benzyl alcohol under conditions no more drastic than those required to hydrolyze (I). The interconversions therefore

[10][a] W. Schlenk and E. Bergmann, *Ann.* **463**, 1 (1928); [b] J. F. Walker and N. D. Scott, *J. Am. Chem. Soc.* **60**, 951 (1938).

appear to be simple displacements. Plausible mechanisms involving the adjacent nitrogen atom may be mentioned without laboring the details. In one, a basic catalyst removes the amide hydrogen to form an iminoketone (Chart 3, A perhaps by way of an intermediate amide anion) which then adds the displacing base by steps which are essentially the reverse of the forward ones. In an other, the adjacent nitrogen atom

Chart 3



facilitates a first-order ionization, perhaps with acid-catalysis, to an iminonium ion (Chart 3, B) which then adds water or the new alcohol in a reversal of the first step. Facile displacements of this type are recorded in the literature.[11,12] Although iminoketones of the sort considered as intermediate have been claimed,[13] no case has been adequately substantiated. One example which might have lead to a system of this type in fact furnished a tautomer.[14]

Compound (I) and presumably (II) also undergoes an interesting transformation to an isomer of (II), $C_{12}H_{11}NO_2$ (IV) on more drastic treatment with alkali. Examination of the ultraviolet spectrum discloses no similarity to those of (I) and (II) but quite close correspondence to that of an α-substituted naphthalene. The infrared spectrum likewise shows marked and significant changes. Whereas (I) and (II) show amide absorption at 5·98 μ (1672 cm^{-1}) amide (I) band and no absorption of the amide (II) type (generally lacking in cyclic lactams), (IV) shows amide (II) absorption at 6·19 μ (1616 cm^{-1}) in addition to the amide (I) type at 5·95 μ (1681 cm^{-1}).[15] Consequently compound (IV) almost certainly contains a primary amide grouping. Oxidation of (IV) with permanganate affords benzene-1:2:3:4-tetracarboxylic acid* and naphthalene-1:4-dicarboxylic acid depending on the conditions. Finally (IV) can be converted to an O-acetate, indicative of the presence of an hydroxyl group.

The structural hypothesis indicated for (IV) in Chart 4 was constructed largely on mechanistic grounds and was proved by independent synthesis. Starting with naphthalene-1:4-dicarboxylic acid (obtained from the dihydro acid, Chart 2, A), the half methyl ester was prepared by partial saponification of the dimethyl ester and converted to the acid chloride (Chart 4, A). Reduction of the acid chloride to the hydroxymethyl compound (Chart 4, B) and conversion of the carbomethoxy grouping to carboxamide by heating with ammonia led to 1-hydroxymethylnaphthalene-4-carboxamide, identical in all respects to (IV), the product of hydrolysis and rearrangement of (I).

A mechanistic rationalization of the formation of (IV) involves the assumption that (I) is first hydrolyzed to (II), as it is on milder treatment with alkali (refer to

* We are most grateful to Dr. F. González-Sánchez, Instituto del Combustible, Zaragoza, Spain, for sending us infrared spectra of the acid and its tetramethyl ester as well as a sample of the pure acid.

[11] A. Dunet and A. Willemart, *Bull. Soc. Chim. Fr.* 887 (1945).

[12] P. C. Jocelyn and A. Owen, *J. Chem. Soc.* 4437 (1957).

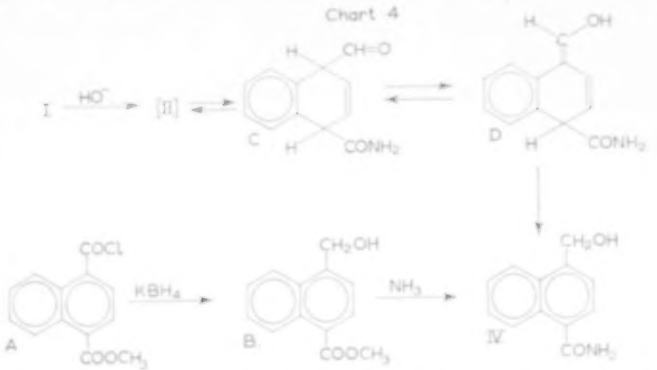
[13] A. Hantzsch, *Ber. Dtsch. Chem. Ges.* **27**, 1248 (1894); F. Feist, *Ibid.* **45**, 945 (1912); A. W. Titherley and M. E. Marples, *J. Chem. Soc.* **93**, 1933 (1908); K. C. Pandya and T. S. Sodhi, *Proc. Indian Acad. Sci.* **7**, 361 (1938).

[14] E. Tagman, E. Surz and K. Hoffmann, *Helv. Chim. Acta* **37**, 185 (1954).

[15] L. J. Bellamy, *The Infrared Spectra of Complex Molecules* pp. 175–189. Methuen, London (1954).

Chart 2), and that (II) is in equilibrium with its open tautomer, the aldehyde amide (Chart 4, C). A series of prototropic rearrangements, perhaps passing over the related enol (Chart 4, D), leads to (IV) in a straightforward way. The rearrangement is an

Chart 4



internal oxidation-reduction reaction whose driving force comes, to a first approximation, from the resonance energy of the new benzene ring.

What there is to say at present about the mechanism of formation of (I) is based on the assumption that the rearrangement of the azide proceeds normally to the *iso*cyanate (Chart 5, A), which then undergoes the unusual transformation to (I). This assumption is supported by the fact that the product of rearranging the carbonyl azide (Chart 1, C) in benzene, in the absence of benzyl alcohol, shows absorption in the infrared at 4·43 μ (2259 cm^{-1}).* The assumption is consistent with the fact that *cyclo*propane carboxylic acid undergoes a normal Hofmann[17] and Schmidt[18] reaction while 2-phenyl*cyclo*propropane carbonyl azide and 2-(3′:4′-dimethoxyphenyl) *cyclo*propane carbonyl azide rearrange normally.[19]

A grossly reasonable mechanism for the rearrangement of the *iso*cyanate can be proposed independent of the stereochemistry. Breaking of the *cyclo*propane bond to the β-carbon atom of the naphthalene ring system leads to the redistribution of the pair of electrons of that bond between two portions (Chart 5, B). In the one portion the unbonded orbital is α to the *iso*cyanate grouping and is itself in resonance with the form in which the carbonyl group of the *iso*cyanate bears the unbonded orbital. This type of resonance, the energetic value of which is not possible to guess either in theory or by analogy with pertinent experimental observations, presumably prevails no matter how the pair of electrons is distributed. In the other portion, the unbonded orbital is involved much as it is in α-substitution reactions of naphthalene. In principle rebonding can now occur between the carbon atom of the *iso*cyanate grouping and the 4-position of the naphthalene ring or the 2-position.

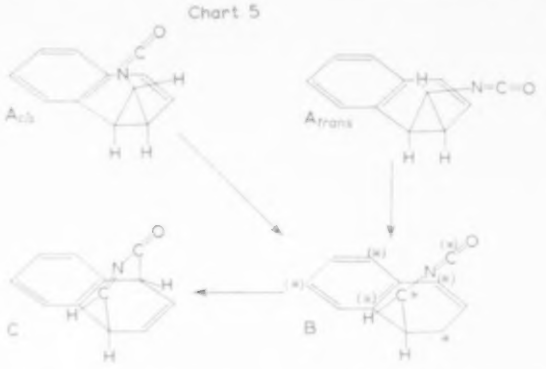
If the *iso*cyanate be *trans* (Chart 5, A_{trans}) as indeed it appears from the isolation by Buchner and Hediger[5] of *trans-cyclo*propane tricarboxylic acid and the established stereochemistry of the Curtius rearrangement, extensive rotation of the *iso*cyanate group is required to rebond at either the 2- or 4-position and the non-bonded system

* 4·40–4·45 μ is reported for the *iso*cyanate grouping.[16]

[16] H. Hoyer, *Chem. Ber.* **89**, 2677 (1956).
[17] P. Lipp, J. Buchkremer and H. Seeles, *Ann.* **499**, 1 (1932).
[18] M. J. Slatter, *J. Am. Chem. Soc.* **63**, 1733 (1941).
[19] A. Burger and W. L. Jost, *J. Am. Chem. Soc.* **70**, 2198 (1948); A. Burger and G. T. Fitchett, *Ibid.* **74**, 3415 (1952).

must be considered to be an intermediate in which the two portions function relatively independently of each other. If contrary to the literature the *iso*cyanate be *cis* (Chart 5, A_{cis}), rearrangement may occur with a remarkably small readjustment of bond

Chart 5



angles and distance through a transition state in which the new bond may be formed simultaneously with the breaking of the old and in which the two portions need never be free (Chart 5, B).*

Overlap simultaneously between C_2 and Cα to N—C—O and between C_4 and carbonyl C of N—C—O (even though unequal in contribution) in the product-determining transition state may account for the overwhelming predominance of bonding at C_4 (Chart 5, C). In this analysis the rearrangement would be encouraged more by a *cis*-configuration of the starting *iso*cyanate than by the *trans* indicated in the literature. The question of stereochemical assignment is under investigation.

In completing a hypothetical mechanism for the formation of (I), the entirely reasonable reaction of the imino ketone (Chart 5, C) with benzyl alcohol must occur. Mechanisms for this reaction have already been considered above and are outlined in Chart 3.

EXPERIMENTAL†

Methyl 1-*Benznorcaradienecarboxylate from Naphthalene and Methyl Diazoacetate*[3]

Following the procedure for the reaction of naphthalene and ethyl diazoacetate,[5] 2800 g (22·5 moles) naphthalene was heated to 150° in a 5-l., three-necked flask fitted with therm, stirrer, water-cooled addition funnel, and two Vigreux columns in series. Over an 8 hr period, 450 g (4·50 moles) methyl diazoacetate was added dropwise during stirring. After being heated an additional 2 hr, the crude product was distilled

* We wish to thank Prof. R. B. Woodward, Harvard University, for emphasising the importance of continuous overlapping of the two positions during the rearrangement.[20]

† All boiling and melting points are uncorrected. The latter were taken on a Kofler micro hot stage. Analyses were performed by Scwarzkopf Microanalytical Laboratories, 56–19 37th Avenue, Woodside 77, New York. Infrared spectra were taken on a Perkin–Elmer Model 21 recording spectrophotometer using sodium chloride optics and were calibrated against the spectrum of atmospheric water. Ultraviolet spectra were taken on a Cary Model 11S recording spectrophotometer.

The n.m.r. spectra were determined using a Varian Associates Model 4300 V High Resolution spectrometer with super-stabilizer and spinning sample. Peak positions are reported in cps at 40 mc relative to benzene.

[20] R. B. Woodward and T. J. Katz, *Tetrahedron* **5**, 70 (1959).

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through a 2 × 30-cm Vigreux column collecting the first fraction, largely naphthalene, at 130–140°/45 mm in an externally cooled, three-necked flask to prevent clogging. The second fraction, 203 g (45%), b.p. 150–152°/6 mm was collected in a water-cooled condenser and receiving flask.

Purified material was obtained by redistillation through a 0·5 × 50-cm, glass-spiral column; b.p. 109°/0·6 mm; n_D^{25} 1·5882. The ultraviolet spectrum (acetonitrile), shown in Fig. 1, had λ_{max} at 222, 228, 235, 271, and 304 mμ (log ε 4·47, 4·52, 4·40, 3·90, and 3·08, respectively).

2-*Benzyloxy*-6:7-*benzo*-3-*azabi*cyclo [3.2.2] *nona*-6:8-*dien*-4-*one* (I)

(1) *By way of* 1-*benznorcaradienecarbonyl hydrazide* (*Hoffman*[3])

A mixture of 55 g methyl 1-benznorcaradienecarboxylate and 150 ml 85% hydrazine hydrate in 300 ml methanol was refluxed for 36 hr. The product, obtained by diluting the cooled solution with water, was recrystallized from ethyl acetate: m.p. 211·0–211·5° (Found: C, 72·2; H, 6·1; N, 14·3. $C_{12}H_{12}N_2O$ requires C, 72·0; H, 6·0; N, 14·0%). A solution of 12 g (0·17 mole) sodium nitrite in the minimum amount of water was added slowly during stirring to a cooled (0°) solution of 30 g (0·15 mole) hydrazide in 400 ml acetic acid containing 100 ml each of benzene and water. The solution was then poured into 1 l. water separating a benzene layer which was washed with water and aqueous sodium bicarbonate and dried over anhydrous sodium sulfate.

The dried solution of azide was diluted to 1 l. with benzene, treated with 40 g (0·37 mole) benzyl alcohol, and refluxed for 7 hr. Removal of the benzene by distillation and trituration of the residue with ether yielded 27 g (61%) of compound (I), m.p. 180–184° after recrystallization from acetone (Found: C, 78·5; H, 5·7; N, 5·0. $C_{19}H_{17}NO_2$ requires C, 78·3; H, 6·0; N, 4·8%).

(2) *By way of* 1-*benznorcaradienecarbonyl chloride*

(a) *Hydrolysis of methyl ester.* A solution of 100 g (0·5 mole) methyl benznorcaradienecarboxylate and 56·1 g (1·00 mole) KOH in 500 ml 40% aqueous ethanol, was refluxed for 3 hr in a nitrogen atmosphere. After being cooled and poured into 1500 ml ice-water, the reaction mixture deposited naphthalene which was filtered. The aqueous filtrate was covered with 1 l. ether and acidified with conc HCl during vigorous stirring. The etheral solution was washed twice with 250-ml portions water, dried over anhydrous sodium sulfate, and concentrated to 81·7 g (88%) of crude 1-benznorcaradienecarboxylic acid, m.p. 168·0–168·2° after recrystallization from ethanol (reported[5] m.p. 165–166°).

To avoid the isolation of ester, the following procedure proved expedient. Most of the excess naphthalene, boiling at 110–120°/38 mm, was distilled from the completed reaction of 2 moles of crude methyl diazoacetate and 10 moles of naphthalene. A solution of 112·2 g (2 moles) KOH in 1500 ml of 50% aqueous methanol was added to the residue and stirred vigorously for 8 hr at reflux. The cooled reaction mixture was poured into 1 l. water and filtered to remove naphthalene. The clear filtrate was acidified during cooling and scratching. After several hours at 5°, the oily acid had become sufficiently crystalline to be filtered, washed, and dried. The yield was 49% of theory based on glycine hydrochloride methyl ester.

(b) 1-*Benznorcaradienecarbonyl chloride*. A solution of 50 g (0·269 mole) 1-benznorcaradienecarboxylic acid and 51·2 g (0·429 mole) thionyl chloride (purified according to Vogel [21]) in 3 l. of anhydrous benzene was refluxed 16 hr. Freed of solvent and excess thionyl chloride *in vacuo*, the product was distilled at 98–100°/0·05 mm as a yellow oil, crystallizing in the receiver; 46·5 g (85%). Recrystallization from pentane at 5° afforded colorless crystals, m.p. 70·0–70·5° (Found: C, 70·4; H, 4·6; Cl, 17·1 $C_{12}H_9ClO$ requires C, 70·4; H, 4·4; Cl, 17·3%).

After having been refluxed for 12 hr, a solution of 15·0 g (0·0732 mole) of the acid chloride in 25 ml methanol was concentrated and fractionally distilled through a 1·5 × 30-cm glass-helix packed column yielding methyl 1-benznorcaradienecarboxylate: n_D^{25} 1·5892; and having an infrared spectrum superimposable on that of a sample prepared directly from naphthalene (*vide supra*).

(c) *Preparation and decomposition of* 1-*benznorcaradienecarbonyl azide*. To a magnetically stirred solution of 31·1 g (0·152 mole) acid chloride in 120 ml acetone cooled in ice, 13·4 g (0·204 mole) sodium azide in 40 ml water was added during 45 min, maintaining the temp below 20°. The precipitated NaCl was filtered and washed with 75 ml benzene. The filtrate and benzene liquid were poured into 750 ml benzene and extracted with 250 ml saturated aqueous sodium bicarbonate, three 250-ml portions water, and 250 ml saturated aqueous sodium chloride. The benzene solution was dried over anhydrous sodium sulfate at 5° prior to decomposition.

To 750 ml of this solution, theoretically containing 0·152 mole of azide, 25·7 ml (0·378 mole) of freshly distilled benzyl alcohol was added. Refluxing for 24 hr afforded 84% of the theoretical amount of nitrogen. Removal of the solvent and most of the benzyl alcohol *in vacuo* left a yellow oil which crystallized upon trituration with ether; 30·17 g (69%). An oil, obtained by evaporation of the ether washings, contained none of the product, as determined by infrared spectrum and was not further investigated.

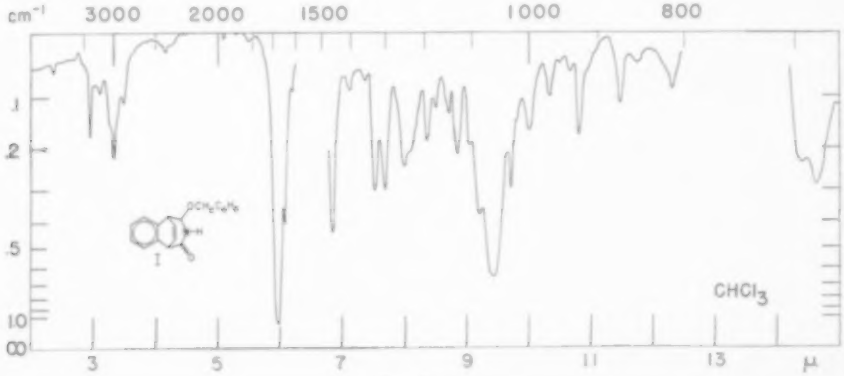

FIG. 2.

(I) is insoluble in ether, benzene, hexane, and carbon tetrachloride, soluble in ethyl acetate, methylene chloride, dioxane, and dimethyl formamide, and slightly soluble in chloroform, acetonitrile and acetone. The crude product may be recrystallized from acetonitrile or acetone. Six recrystallizations from acetone furnished

[21] A. I. Vogel, *A Textbook of Practical Organic Chemistry* p.185. Longmans, Green and Co., New York (1951).

colorless crystals, m.p. 183–187° (Found: C, 78·4; H, 5·7; N, 4·8. $C_{19}H_{17}NO_2$ requires C, 78·3; H, 6·0; N, 4·8%). A mixture with the sample, m.p. 180–184°, prepared above, melted at 182–186°.

When the decomposition was carried out in the absence of benzyl alcohol, the benzene solution yielded oily crystals, decomposing slowly at room temp. The infrared spectrum of this material, taken in chloroform, disclosed typical *iso*cyanate absorption at 4·43 and 5·92 μ.* All attempts to recrystallize led to decomposition and disappearance of these bands.

(I) is unsaturated to permanganate, gives a negative Tollens test, and is insoluble in neutral, acidic, or alkaline water. The ultraviolet spectrum in acetonitrile, shown in Fig. 1, has λ_{max} 258 and 270 mμ (log ϵ 2·63 and 2·35, respectively). In the infrared, NH and carbonyl absorption occur at 2·97, 3·14, and 6·00 μ in chloroform, 2·95, 3·13, and 6·01 μ in potassium bromide, and 2·85, 3·08, and 5·98 μ in dioxane.

Lithium aluminum hydride reduction of (I)[3]

A solution of 800 mg (2·75 mmoles) of (I) in 20 ml tetrahydrofuran, freshly distilled from butyl magnesium bromide, was added to a stirred slurry of 155 mg (4·14 mmoles) lithium aluminum hydride in 20 ml of the same solvent in a nitrogen atmosphere. After being stirred 24 hr, the reaction mixture was refluxed 1 hr, cooled in ice, diluted with 2 ml water in 10 ml tetrahydrofuran and centrifuged. The supernatant liquid was decanted into water and extracted with chloroform. The chloroform extracts were washed with water and extracted with 3 M HCl. The acid extracts were neutralized and re-extracted with chloroform. Finally the chloroform solution was dried over anhydrous potassium carbonate and evaporated *in vacuo* to a residue which yielded on evaporative distillation 158·5 mg (34%) amine as a pink oil.

The N-*phenylthiourea* was prepared by Hoffmann[3] from the amine and phenyl *iso*thiocyanate and recrystallized from ethanol-water (Found: C, 74·7; H, 5·6; N, 8·9; S, 10·5. $C_{19}H_{18}N_2S$ requires C, 74·5; H, 5·9; N, 9·1; S, 10·5%).

The N, N-*dimethyl ammonium iodide* was prepared (Hoffmann), by treating 1 g (5·86 mmoles) of the amine above with 1 g (7·25 mmoles) potassium carbonate and 1 g (7·06 mmoles) methyl iodide in 7 ml chloroform. After the exothermic reaction had subsided, the solution was kept for 24 hr. Washing the crude product with chloroform afforded 1·3 g of colourless crystals which upon recrystallization from chloroform, m.p. 200–201° with dec. (Found: C, 51·1; H, 5·7; I, 38·8; N, 4·0. $C_{14}H_{18}IN$ requires C, 52·6; H, 5·5; I, 38·8; N, 4·3%).

A slurry of 130 mg (0·41 mmole) of the ammonium salt and 100 mg (2·5 mmoles) sodium hydroxide in 800 mg ethylene glycol was refluxed for 1 min and cooled. Extraction with pentane and concentration of the pentane left 70 mg of an oil which was treated with methyl iodide as above to give 100 mg of quaternary ammonium salt, m.p. 201–202° with dec; mixed m.p. with starting material of m.p. 200·2–200·8° was 194·0–200°.

Benznorcaradiene

(a) *The reaction of naphthalene with diazomethane.*[3] A solution of 2·38 kg (18·5 moles) naphthalene in 6·84 l. benzene was prepared in two 5-l. flasks lacking ground glass surfaces and equipped with motor-driven, glass stirrers. A total of 495 ml

* 4·40–4·45 μ is reported for the *iso*cyanate grouping.[10]

(3·54 moles) 40% aqueous KOH was added to both flasks which were then cooled to −5° by ice and salt. Over the course of 2·5 hr, 291 g (2·82 moles) N-nitroso-N-methylurea[22] was added in small portions, maintaining the temperature below 0° during vigorous stirring. The contents of the flasks were allowed to warm to 15° and the organic layers were decanted onto KOH pellets and dried for 4 hr while cooled in ice. The benzene solution was then transferred to two similar 5-l. flasks, fitted with drying tubes containing KOH and cooled by an external stream of water. Irradiation, by six Westinghouse, type RS sunlamps, was continued until nitrogen evolution ceased. This required 18 to 36 hr depending on the age of the bulbs.

Attempts to separate benznorcaradiene from naphthalene by careful fractional distillation were frustrated by the solidification of naphthalene. Benzene was distilled from the combined solutions through a 2 × 95-cm Stedman column until the volume of material in the pot had been halved. Naphthalene crystallized on cooling and was filtered and washed with pentane. The combined washings and filtrate were reconcentrated. This process of concentration, cooling, filtration of the naphthalene, and reconcentration of the filtrate was repeated four or five times until no more naphthalene would precipitate from the concentrate at 0°.

The final, dark, oily concentrate was steam-distilled to give a condensate of naphthalene crystals and liquid benznorcaradiene from which the naphthalene was removed by filtering. A pentane extract of the filtrate was dried over anhydrous sodium sulfate and concentrated to crude benznorcaradiene.

(b) *Benznorcaradiene dibromide.*[3] To a solution of 35 g of crude benznorcaradiene in 300 ml carbon tetrachloride, cooled to −25°, 40 g bromine in 300 ml of the same solvent was added over a 1-hr period, maintaining a reaction temperature of −25 to −20° during stirring. Evaporation of the solvent and excess bromine at room temp, *in vacuo*, afforded a viscous oil which was extracted with 900 ml hexane in several portions. On concentrating the washings to 120 ml at room temp and cooling to 0°, the dibromide crystallized. The first two crops of colorless crystals weighed 17·27 g (1·7%, based on nitrosomethylurea; in several experiments, the yield varied from 1·5–2·5%); m.p. 85·8–86·8° with dec. This material can be kept indefinitely at −78° but decomposes slowly at room temp making it impossible to obtain satisfactory analyses (Found: C, 41·7; H, 3·8; Br, 42·1. $C_{11}H_{10}Br_2$ requires C, 43·7; H, 3·3; Br, 52·9%).

(c) *Debromination of benznorcaradiene dibromide.*[3] A 150-ml portion ether, freshly distilled from *n*-butyl magnesium bromide, and 8·45 g (0·130 g-atom) zinc dust were placed in a 500-ml, three-necked flask equipped with a pressure compensating addition funnel, stirrer, and reflux condenser protected from atmospheric moisture. A few ml of a solution of 16·9 g (0·0562 mole) recrystallized dibromide in 150 ml ether, freshly distilled as above, were added during vigorous stirring. Heat was carefully applied to initiate the exothermic reaction and then removed. The dibromide solution was added at such a rate that the ether was maintained at gentle reflux. After the addition, the solution was stirred for an additional 12 hr, and filtered to remove unreacted zinc. The filtrate was washed with 50 ml 3 M HCl, three 50-ml portions water, 50 ml saturated aqueous sodium chloride, and dried over anhydrous sodium sulfate. Evaporation of solvent, followed by distillation through a 0·5 × 50-cm, glass-spiral

[22] C. R. Noller and S. Lieberman, *Organic Syntheses*, Coll. Vol. II, p. 461. John Wiley and Sons, Inc., New York.

column, afforded 6·11 g (75%) of *benznorcaradiene*, collected at 96–97°/6·5 mm. A center cut, b.p. 96·5°/6·5 mm, had n_D^{25} 1·6056 (Found: C, 93·1; H, 7·4; C-methyl "very small, could be 0". $C_{11}H_{10}$ requires C, 92·9; H, 7·1; C-methyl, 0%).

Benznorcaradiene exhibits λ_{max} at 222, 274, and 306 mμ (log ϵ 4·19, 3·82, and 3·02, respectively) in hexane, shown in Fig. 1, and 221, 274, and 306 mμ (log ϵ 4·32, 3·81, and 3·02, respectively) in 95% ethanol.

2-(o-Carboxyphenyl)-cyclopropanecarboxylic acid

The oxidative procedure employed is based on that of Lemieux and von Rudloff.[23] A solution of 50 mg (0·352 mmole) benznorcaradiene in 20 ml dioxane, distilled from permanganate and dried over potassium hydroxide, was diluted to 70 ml with water and treated with 35 mg (0·25 mmole) potassium carbonate, 634 mg (2·76 mmoles) potassium metaperiodate, and 7·5 mg (0·047 mmole) potassium permanganate. Within 4 hr at room temp with magnetic stirring, the permanganate had been reduced and a few more crystals were added. After an additional 24 hr, the manganese dioxide was filtered. The clear filtrate was acidified with 2 ml of 3 M HCl and extracted continuously with ether. Drying of the extract over anhydrous sodium sulfate and and evaporation of the solvent gave material which was sublimed at 120°/0·003 mm yielding 20·7 mg (29%) of colorless crystals, m.p. 192–200°. Material recovered from the titration was sublimed at 120°/0·005 mm and recrystallized (Found: C, 63·9; H, 4·8; neut. equiv. 106·9. $C_{11}H_{10}O_4$ requires C, 64·1; H, 4·9%; neut. equiv. 103·1).

*2-Hydroxy-6:7-benzo-3-azabi*cyclo [3.2.2] *nona-6:8-dien-4-one* (II)

Two grams (6·88 mmoles) of (I) were added to a solution of 1·6 g (28·6 mmoles) potassium hydroxide in 25 ml ethanol and the slurry was stirred magnetically for 12 hr in a nitrogen atmosphere. Unreacted (I) was recovered by filtering: 870 mg (40%). The recovery of starting material and yield of product was sensitive to the presence of impurities in the former and to the presence of air, both factors tending to decrease both the recovery and the yield but resulting in an increase in the percent conversion.

The ethanolic filtrate was poured into 75 ml saturated aqueous sodium chloride and continuously extracted with ether. Removal of the ether and its dissolved ethyl and benzyl alcohols, finally *in vacuo*, furnished a viscous residue which was extracted with 25 ml boiling toluene. Concentration of the toluene solution yielded 701·1 mg (90% based on unrecovered I) of (II) which was recrystallized from toluene: m.p. 183–191·5° with dec. (Found: C, 71·9; H, 5·5; N, 7·0 $C_{12}H_{11}NO_2$ requires C, 71·6; H, 5·5; N, 7·0%): ultraviolet spectrum in acetonitrile: λ_{max} 262 and 271 mμ (log ϵ 2·28 and 2·16, respectively); infrared spectrum in potassium bromide: 3·14, 3·27, and 6·00 μ; in dioxane: 2·84, 3·04, and 5·98 μ.

(II) could not be converted to an acetate or α-naphthyl urethane; it did give positive permanganate and Tollens tests.

Reconversion of (II) *to* (I). A solution of 100 mg of (II) and 10 ml freshly distilled benzyl alcohol in 40 ml anhydrous benzene was refluxed in a Dean–Stark water-separation apparatus in a nitrogen atmosphere. After 12 hr, benzene and excess benzyl alcohol were removed *in vacuo* leaving an oil which was triturated with ether (86·5 mg; 60%). One recrystallization from acetone gave (I), m.p. 178–187° alone

[23] R. U. Lemieux and E. von Rudloff, *Canad. J. Chem.* **33**, 1701, 1710, 1714 (1955).

and 175·5–181·5° in admixture with a sample of (I), m.p. 180–184°. Infrared spectra of the two samples were superimposable.

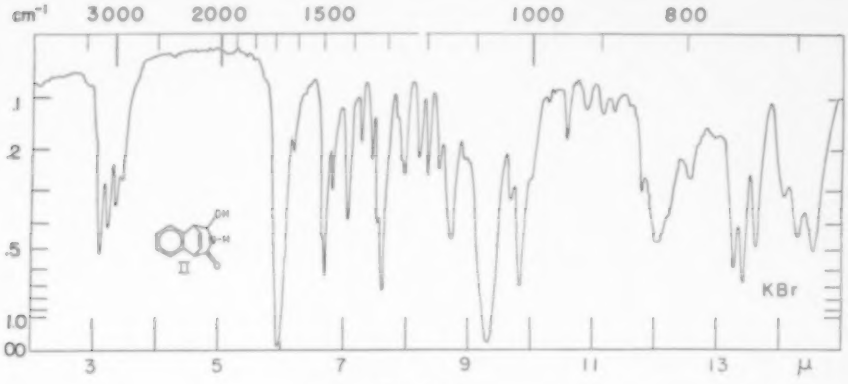

FIG. 3.

Hydrogenation of (II). Catalytic hydrogenation at atmospheric pressure of 201 mg of (II) in 35 ml ethyl acetate with 90 mg 5% palladium-on-charcoal, proceeded with the rapid uptake of 1·01 equivalents of hydrogen. Filtration and concentration afforded 199 mg of colorless crystals which could be recrystallized (but ineffectively purified) from *cyclo*hexane; m.p. 129·0–133·0° (Found: C, 71·9; 71·8; H, 7·0; 7·1; N, 6·7; 6·5. $C_{12}H_{13}NO_2$ requires C, 70·9; H, 6·5; N, 6·9%).

Hydrogenation of 2-*benzyloxy*-6:7-*benzo*-3-*aza*bicyclo-[3.2.2]*nona*-6;8-*dien*-4-*one* (I)[3]

A solution of 900 mg of (I) in 70 ml ethyl acetate was hydrogenated at atmospheric pressure using 450 mg 5% palladium-on-charcoal as catalyst. Within 16 min, 0·94 equivalents hydrogen were consumed. Removal of the catalyst and evaporation of the solvent left a colorless oil. Trituration with pentane furnished 704·5 mg (78%) of colorless crystals of 2-*benzyloxy*-6:7-*benzo*-3-*aza*bicyclo [3.3.2] *nona*-6-*en*-4-*one*. This material no longer decolorized permanganate and was soluble in carbon tetrachloride and benzene but not in hexane. Recrystallization from *cyclo*hexane gave material; m.p. 145–146·5° (Found: C, 78·0; H, 6·8; N, 4·6. $C_{19}H_{19}NO_2$ requires C, 77·8; H, 6·5; N, 4·8%).

Ultraviolet spectrum in acetonitrile λ_{max} 247, 251, 253, and 259 mμ: (log ϵ 2·67, 2·65, 2·65, and 2·45, respectively); the infrared spectrum showed NH and carbonyl absorption at 2·97, 3·14, and 6·00 μ in chloroform and 2·93, 3·08, and 5·99 μ in dioxane.

When the hydrogenation was repeated in acetic acid as solvent, 2·1 equivalents of hydrogen was absorbed, the first half far more rapidly than the second. However, only amorphous material could be isolated. The hydrolysis of dihydro-I was attempted both at reflux and at room temp using a solution of 300 mg and 252 mg KOH in 3·6 ml ethanol. All efforts to isolate a crystalline product failed. In one experiment, performed at reflux, benzyl alcohol could be detected as one of the components of the crude reaction product by infrared spectroscopy.

Chromic acid oxidation of (II): 1:4-*dihydro*-1:4-*naphthalenedicarboximide*

The procedure employed is a modification of that used by Henbest, et al.[24] To a solution of 1·0 g of (II) in 200 ml acetone, 1 ml 2·67 M chromic acid was added dropwise during magnetic stirring. The oxidant was prepared by dissolving 6·67 g chromium trioxide in the minimal amount of water, adding 5·3 ml conc H_2SO_4 and diluting the solution to 25 ml with water. After 5 min stirring, excess chromic acid was destroyed by a few ml of a saturated solution of sulfur dioxide in acetone. The reduced solution, containing a colloidal dispersion of chromic salts, was filtered from the precipitated salts, treated with an equal volume of ethyl acetate, extracted with three 50-ml portions saturated aqueous potassium carbonate and 25 ml saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and concentrated to yield 701 mg (71%) of crude imide. *cis*-1:4-Dihydro-naphthalenedicarboximide was insoluble in benzene and could be recrystallized from toluene; m.p. 240·0–240·5° (in a sealed capillary; otherwise sublimation begins about 200°) (Found: C, 72·5; H, 4·7; N, 7·3. $C_{12}H_9NO_2$ requires C, 72·6; H, 4·6; N, 7·0%); infrared spectrum disclosed significant peaks at 3·13, 5·85, and 5·93 μ in potassium bromide and 3·22 and 5·84 μ in dioxane.

1:2:3:4-*Tetrahydro*-1:4-*naphthalenedicarboximide* (III)

Catalytic hydrogenation of 701 mg of the unsaturated imide above in 95 ml ethyl acetate at atmospheric pressure using 500 mg 5% palladium-on-charcoal, proceeded with the consumption of 0·908 molar equivalents of hydrogen. The addition of filter-aid was followed by filtration and evaporation of solvent. Recrystallization from benzene furnished crystals, m.p. 206·5–207·0° in a sealed capillary (Found: C, 71·9; H, 5·7; N, 7·0. $C_{12}H_{11}NO_2$ requires C, 71·6; H, 5·5; N, 7·0%); infrared spectrum in potassium bromide: 3·16, 5·86, and 5·94 μ.

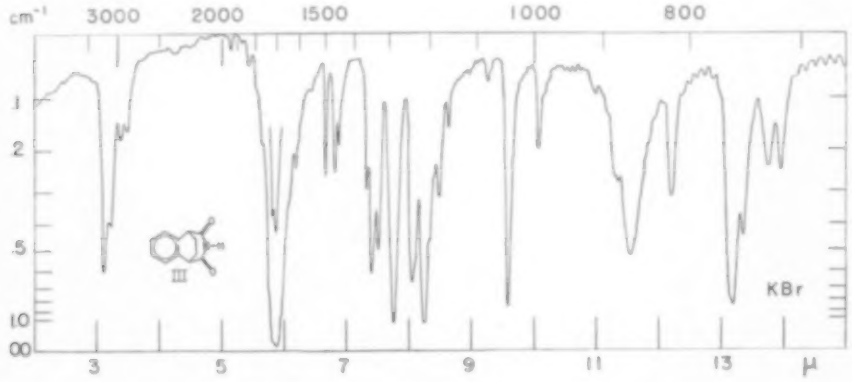

FIG. 4.

Synthesis of authentic 1:2:3:4-*tetrahydro*-1:4-*naphthalenedicarboximide* (III)

(a) 1:2:3:4-*Tetrahydro*-1:4-*naphthalenedicarboxylic anhydride*. A solution of 10 g 1:4-dihydro-1:4-naphthalenedicarboxylic acid,[10(b)] m.p. 200–210°, in 300 ml acetic acid

[24] P. Bladen, J. M. Fabian, H. B. Nenbest, H. P. Koch and G. W. Wood, *J. Chem. Soc.* 2407 (1951).

was hydrogenated at 40 p.s.i. using 50 mg platinum oxide as catalyst. Filtration of the catalyst, followed by evaporation of the solvent *in vacuo*, afforded 8·60 g 1:2:3:4-tetrahydro-1:4-naphthalenedicarboxylic acid, of which the ultraviolet spectrum in acetonitrile (λ_{max} 263 mμ, log ϵ 2·71) was quite similar to that of starting material: (λ_{max} 262 mμ, log ϵ 2·02).

A solution of 2·0 g of this diacid in 6·0 ml acetic anhydride was heated for 1 hr at 100° and concentrated *in vacuo* at room temp to a viscous oil. Sublimation at 130°/0·05 mm afforded 1·18 g (65%) of the anhydride as colorless crystals exhibiting characteristic infrared absorption at 5·60 and 5·70 μ in potassium bromide; m.p. 107·5–112°, solidifying and remelting at 154·5–162·5° (Found: C, 71·5; H, 5·1. $C_{12}H_{10}O_3$ requires C, 71·3; H, 5·0%).

(b) 1:2:3:4-*Tetrahydro*-1:4-*naphthalenedicarboximide*. Five hundred milligrams of the anhydride was cautiously dissolved in 20 ml concentrated aqueous ammonia in a 50-ml round-bottomed flask. A 2 × 15-cm Vigreux column was attached as an air condenser and the flask was heated in a Wood's metal bath. After boiling away the ammonia and water, the temp was slowly raised to 300° and maintained there for 1 hr. The cooled reaction product was extracted with 25 ml of refluxing benzene to yield, on concentration, 460 mg (94%) of crude (III). Insoluble in *cyclo*hexane and carbon tetrachloride, this material could be recrystallized from either ethyl acetate or benzene, the latter solvent furnishing colorless crystals of m.p. 205·5–206·0° in a sealed capillary; mixed m.p. with the sample above, 206·5°; infrared spectra of the two samples were superimposable (Found: C, 71·9; H, 5·6; N, 6·9. $C_{12}H_{11}NO_2$ requires C, 71·6; H, 5·5; N, 7·0%).

Hydrolysis of (I) *to* 4-*hydroxymethyl*-1-*naphthamide*

A solution of 20·0 g of (I) and 16 g KOH in 250 ml ethanol was refluxed 1 hr in a stream of dry nitrogen and then poured into 1·5 l. saturated aqueous sodium chloride. Continuous extraction by ether followed by concentration, ultimately at 0·005 mm for 8 hr furnished a viscous residue. One recrystallization from acetone gave 9·62 g (70%) of 4-hydroxymethyl-l-naphthamide. In another experiment, the alcoholic reaction mixture was diluted with water and extracted with ether. The dried extract was concentrated and evaporatively distilled at 85° and 45 mm to give benzyl alcohol in 56% of theory, identified by infrared spectrum. The hydroxyamide is insoluble in benzene or chloroform and slightly soluble in ether, water, acetonitrile and acetone. Three recrystallizations from acetone, followed by sublimation at 120° and 0·02 mm, afforded 4-hydroxymethyl-1-naphthamide with the following melting characteristics. Sublimed material always melts at 152–153·5°. Recrystallized material shows a phase transition beginning at 143·5° from prism to needles which under the polarizing microscopic appears as a change from colorless prism (presumably anistropic) to colored, highly refractive needles. The needles then melt at 152–153·5°. The substance gives negative permanganate and Tollens tests and cannot be hydrogenated at an appreciable rate in ethyl acetate with 5% palladium-on-carbon; λ_{max} 226 and 285 mμ (log ϵ 4·78 and 3·88 respectively); NH and carbonyl absorption in the infrared: 3·00, 3·17, 6·08 and 6·20 μ in potassium bromide and 2·93, 5·95 and 6·19 μ in dioxane (Found: C, 71·9; H, 5·8; N, 7·3. $C_{12}H_{11}NO_2$ requires C, 71·6; H, 5·5; N, 7·0%).

The *acetate* could be prepared by dissolving 200 mg of the hydroxyamide in 2 ml

pyridine and 0·8 ml acetic anhydride during cooling. After 24 hr at room temp, the crystalline product was filtered, washed with water, dried, and recrystallized from ethyl acetate; m.p. 198·5–200·0° (Found: C, 69·1; H, 5·6; N, 6·1 $C_{14}H_{13}O_3N$ requires C, 69·1; H, 5·4; N, 5·8%). Its infrared spectrum in dioxane solution showed the expected absorption in the 6 μ region; *viz.* 5·74, 5·94, and 6·20 μ corresponding to acetate carbonyl and amide (I) and (II), respectively; as well as the expected shift of C—O frequency from 9·30 to 8·04 μ (in potassium bromide).

Permanganate-oxidation of 4-*hydroxymethyl*-1-*naphthamide*

(a) 1:2:3:4-*benzenetetracarboxylic acid.* The procedure employed is a modification of that described for the oxidation of 1:4-naphthalenedicarboxylic acid.[25] To a stirred slurry of 150 mg (0·748 mmole) 4-hydroxymethyl-1-naphthamide and 21 mg (0·374 mmole) KOH in 10 ml water, 1·18 g (7·48 mmoles) potassium permanganate was added *slowly*. The contents were stirred for one hour at room temp and then for two at 90°.

After the destruction of excess permanganate with methanol, the manganese dioxide was filtered and washed with 20 ml hot water. Treatment of the filtrate with 307 mg (1·5 mmoles) barium chloride dihydrate gave a precipitate which was digested for 2 hr on the steam bath. Upon filtering the barium salt, 159 mg (1·5 mmoles) sodium carbonate was added to the filtrate, precipitating barium carbonate which was digested, filtered, and combined with the barium salt.

The combined precipitate was then treated with 1 ml of 1·47 M H_2SO_4 at 70° for 12 hr. After removing the barium sulfate and washing with water, the filtrate and washings were concentrated to 0·1 ml when crystals began appearing. The solution was cleared when two drops 1 M HCl were added and was kept at 5° for 12 hr, giving 7·4 mg crude 1:2:3:4-benzenetetracarboxylic acid of m.p. 224·5–237° (dec.); reported,[25] m.p. 236–238°. Concentration of the mother liquors afforded an additional 2 mg bringing the total yield to 5·0% of theory.

Because of the report that the m.p. of this acid is a poor criterion of purity,[26] the *tetramethyl ester* was prepared by treating the crude acid, in methanol, with ethereal diazomethane. Filtration, evaporation of the filtrate, and two recrystallizations afforded ester, m.p. 131·0–133·0°; m.p. 131·5–132·0° in admixture with an authentic sample of tetramethyl 1:2:3:4-benzenetetracarboxylate of m.p. 132·5–133·5°; infrared spectra of the two esters were superimposable.

(b) 1:4-*Naphthalenedicarboxylic acid.* A slurry of 1·50 g (7·48 mmoles) 4-hydroxymethyl-1-naphthamide in 100 ml water containing 3·55 g (22·5 mmoles) potassium permanganate was stirred at room temp for 1 hr and then at 80° for two. Manganese dioxide was filtered with the aid of Super-cel and washed with 100 ml hot water. The alkaline filtrate and washings were concentrated to 25 ml on the steam bath and, after the addition of 3 ml 2·5 M NaOH, refluxed for 48 hr. Acidification afforded 934 mg (58%) of dicarboxylic acid as finely divided white crystals. Sublimation at 150° and 0·005 mm followed by crystallization from acetic acid gave material of m.p. 309·0–327·5° in a sealed capillary; reported m.p. 325°.[27]

The *dimethyl ester* was prepared by treating a slurry of the di-acid, in methanol,

[25] L. I. Smith and E. J. Carlson, *J. Am. Chem. Soc.* **60**, 290 (1939).
[26] F. González-Sánchez, *Tetrahedron* **1**, 231 (1957).
[27] G. Lock and R. Schneider, *Chem. Ber.* **84**, 639 (1951).

with excess ethereal diazomethane. Filtration, evaporation of solvent, and recrystallization from pentane afforded crystals of m.p. 67·5–68·0°; m.p. 67·5–68·0° in admixture with an authentic sample (*vide infra*) of m.p. 68·0–68·5°. Infrared spectra of the two esters were superimposable.

Synthesis of authentic 4-*hydroxymethyl*-1-*naphthamide*

1:4-Naphthalenedicarboxylic acid (3·0 g), prepared according to the procedure of Walker and Scott[10(b)] from dihydro acid (*vide supra*), was treated with excess ethereal diazomethane. Filtration and evaporation yielded the crystalline dimethyl ester which was dissolved in methanol (25 ml) for the next step, but which, in a separate experiment was isolated and recrystallized from pentane; m.p. 60–67·5° (90%) after one recrystallization; m.p. 68·0–68·5° (reported[28] 66·5°) after the third recrystallization. Addition of potassium hydroxide (900 mg) in methanol (3 ml) to the methanolic solution of dimethyl ester followed by refluxing for 1 hr, gave a solution which was poured into ice-water (30 ml) and extracted with three 20-ml portions ether. The combined ethereal extracts were washed with three 20-ml portions water and saturated aqueous sodium chloride (20 ml). Evaporation of the ether afforded 812·6 mg (24% recovery) dimethyl ester. The ether-extracted, aqueous, alkaline solution was heated to remove last traces of ether and acidified to furnish 2·03 g of crystalline *methyl hydrogen* 1:4-*naphthalenedicarboxylate* (64% of theory based on starting 1:4-naphthalenedicarboxylic acid). The infrared spectrum of this material, in potassium bromide, exhibited carbonyl absorption at 5·78 and 5·90 μ (ester and acid, respectively).

Monomethyl ester (1·0 g) was added cautiously to 10 ml of purified[29] thionyl chloride and refluxed 1 hr. Excess thionyl chloride was removed *in vacuo* leaving crude *methyl* 4-*chlorocarbonyl*-1-*naphthoate*, which was dissolved in purified dioxane[30] (10 ml) and treated with potassium borohydride (700 mg). This slurry was refluxed, stirring magnetically, for 3 hr while protected by a calcium chloride-filled drying tube. Water (20 ml) was added, cautiously at first, during stirring. The last traces of borohydride were finally decomposed by the addition of 3 M HCl in an amount insufficient to neutralize the alkaline solution. The aqueous solution was diluted further with water (10 ml) and extracted with three 10-ml portions methylene chloride. The combined extracts were washed with three 20-ml portions water and dried over anhydrous magnesium sulfate. Evaporation afforded 759 mg methyl 4-hydroxymethyl-1-naphthoate as an oil which crystallized on cooling and scratching; yield, 81% based on methyl 1:4-naphthalenedicarboxylate or 71% based on 1:4-naphthalenedicarboxylic acid.

A solution of methyl 4-hydroxymethyl-1-naphthoate (354·3 mg) in methanol (25 ml) was saturated with anhydrous ammonia at 0°, sealed in a Carius tube and heated at 131° for 24 hr. Methanol and excess ammonia were evaporated, finally *in vacuo*, furnishing a brown oily mixture of product and starting material. The former could be separated by crystallization from chloroform-acetone. Charcoal decolorization, followed by recrystallization from acetone afforded 4-hydroxymethyl-1-naphthamide; m.p. 151·5–152·0°, exhibiting the characteristic phase transition at 143·5° (*vide supra*); mixed m.p. with the sample described above was 150·0–151·5°.

[28] E. F. Bradbook and R. P. Linstead, *J. Chem. Soc.* 1739 (1936).
[29] D. L. Cottle, *J. Am. Chem. Soc.* **68**, 1380 (1946).
[30] K. Hess and H. Frahm, *Ber. Dtsch. Chem. Ges.* **71**, 2627 (1938).

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THE MECHANISM OF THE DIELS–ALDER REACTION

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THE combination (I) of the termini of a system of two conjugated double bonds with those of a single unsaturated center—universally known as the Diels–Alder reaction—

I

is one of the most useful of synthetic reactions.[1] In systems activated by appropriate substitution, the reaction proceeds smoothly, often spontaneously, and is little affected by extramolecular circumstances. This fact, and the very nature of the change, ensure that a detailed understanding of the course of the reaction must involve questions of much subtlety. None the less, if only because the reaction constitutes one of the simplest of known bond-forming processes, its detailed mechanism deserves, and has gotten, much attention. The views which have been put forward fall into one or the other of two categories. In the one, the central thesis is that the reaction takes place in *two* steps, the first of which is rate-controlling, and comprises the formation of one single bond (*a* in the intermediate II) between appropriate atoms of the reaction partners; the process is then completed by subsequent formation of a second bond.[2]

II

Those who hold the alternative view maintain that the combination involves the simultaneous formation of the two new single bonds which appear in the product.[3]

[1] J. A. Norton, *Chem. Rev.* **31,** 319 (1942); M. C. Kloetzel, *Organic Reactions* Vol. IV, p.1. Wiley, New York (1948); H. L. Holmes, *Ibid.* Vol. IV, p. 60; L. W. Butz and A. W. Rytina, *Ibid.* Vol. V, p. 136 (1949); K. Alder, *Newer Methods of Preparative Organic Chemistry* p. 381. Interscience, New York (1948); K. Alder and Marianne Schumacher, *Fortschr. Chem. Naturstoffe* **10,** 1 (1953).

[2][a] R. Robinson, *Outline of an Electrochemical (Electronic) Theory of the Course of Organic Reactions* p. 29. The Institute of Chemistry of Great Britain and Ireland, London (1932); [b] G. B. Kistiakowsky and J. R. Lacher, *J. Amer. Chem. Soc.* **58,** 123 (1936); [c] J. B. Harkness, G. B. Kistiakowsky and W. H. Mears, *J. Chem. Phys.* **5,** 682 (1937); [d] G. B. Kistiakowsky and W. W. Ransom, *Ibid.* **7,** 725 (1939); [e] E. C. Coyner and W. S. Hillman, *J. Amer. Chem. Soc.* **71,** 324 (1949); [f] W. E. Bachmann and N. C. Deno, *Ibid.* **71,** 3062 (1949); [g] C. W. Smith, D. G. Norton and S. A. Ballard, *Ibid.* **73,** 5273 (1951); [h] J. S. Meek, B. T. Poon, R. T. Merrow and S. J. Cristol, *Ibid.* **74,** 2669 (1952).

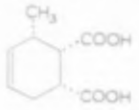
[3][a] K. Alder and G. Stein, *Angew. Chem.* **50,** 510 (1937); [b] A. Wassermann, *Trans. Faraday Soc.* **34,** 128 (1938); [c] A. Wassermann, *Ibid.* **35,** 841 (1939); [d] B. J. F. Hudson and R. Robinson, *J. Chem. Soc.* 715 (1941); [e] A Wassermann, *Ibid.* 612 (1942); [f] F. Bergmann and H. E. Eschinazi, *J. Amer. Chem. Soc.* **65,** 1405 (1943); [g] R. B. Woodward and H. Baer, *Ibid.* **66,** 645 (1944); [h] H. Henecka, *Z. Naturf.* **4B,** 15 (1949); [i] K. Alder, Marianne Schumacher, and O. Wolff, *Liebigs Ann.* **564,** 79 (1949); [j] W. Rubin and A. Wassermann, *J. Chem. Soc.* 2205 (1950); [k] K. Alder, *Liebigs Ann.* **571,** 157 (1951); [l] R. D. Brown, *Quart. Rev.* **6,** 63 (1952); [m] B. Eisler and A. Wassermann, *J. Chem. Soc.* 979 (1953); [n] C. K. Ingold, *Structure and Mechanism in Organic Chemistry* p. 711. Cornell University Press, New York (1953).

The evidence which has been brought forward in support of these proposals is of three kinds. Above all, the magnificent systematic investigations of Alder[3(a,i,k)] established a series of remarkable stereochemical generalizations which have led most chemists to favor the single-step mechanism. Then, the kinetic and thermodynamic investigations, especially those of Wassermann,[3(b,c,e,i,m)] have usually been adduced in favor of a similar choice. On the other hand, the effects brought about by substituents attached to the reacting unsaturated centers have generally been regarded as providing support for the two-step mechanism.[2]

It is the purpose of the present paper to put forward a novel view of the mechanism of the Diels–Alder reaction, which circumvents the difficulties while incorporating the features of merit of each of the previous proposals.

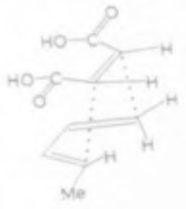
STERIC CONSIDERATIONS

The stereochemical factors attendant upon the Diels–Alder reaction may be summarized in two principles. (1) The stereometrical relationships of groups attached to the diene and to the olefin are, as nearly possible, maintained in the product. (2) If two modes of combination, leading to different steric results, are possible, that one is favored which results from maximum accumulation of unsaturated centers in the presumed activated complex. To exemplify, when *trans* piperylene combines with maleic acid, the reaction proceeds to give the product (III). In accordance with principle (1), the carboxyl groups of the product are on the same side of the newly

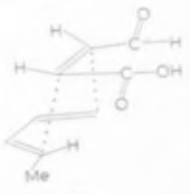


III

formed six-membered ring, as they were on the same side of the double bond in the reactant. Further, in accordance with principle (2), the product is that which would result from the union of the components in the sense (IV), rather than (V). Similarly,



IV



V

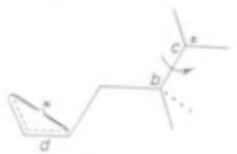
the dimerization of *cyclo*pentadiene, under mild conditions, gives only the *endo* product (VI), through an assumed complex (VII). It should be emphasized at this

VI

VII

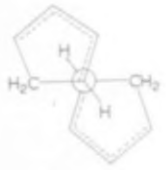
point that while the principle of maximum accumulation of unsaturated centers is in the first instance empirical, it has been given physical meaning through the proposal[3(c),4] that electrostatic and electrodynamic attractive forces associated with the mobile electronic systems not directly involved in the bond-forming processes lower the energy of intermediates such as (IV) and (VII), as compared with the alternatives of the type (V). A very great number of cases have been investigated, and the virtually universal predictive success of the above principles, applied as exemplified here, has been the major factor in bringing about acceptance of the one-step mechanism for the Diels–Alder reaction.

By contrast, the two-step mechanism, in the form in which it has been discussed previously, seems quite incapable of accomodating the stereochemical observations. For, once the initial barrier has been traversed, and the intermediate (VIII) reached,



VIII

free rotation about the bond *bc* would permit dissolution of the original stereometrical relationships of the groups attached to the atoms *b* and *c*. Furthermore, if the repulsive forces of steric demand are alone operative in determining which of the available conformations will be assumed at the barrier in the initial bond-forming process, we may not doubt that in the case of *cyclo*pentadiene, for example, the activated complex will possess the structure (IX). This array leads uniquely to the



IX

X

exo dimer (X), rather than to the observed *endo* product (VI).

THERMODYNAMIC CONSIDERATIONS

Although the great difficulties associated with calculating the entropy of activated states having incompletely known geometric and other properties has led to a certain amount of controversy,[2(d),3(e)] the burden of the kinetic and thermodynamic studies on the Diels–Alder reaction is that the relatively small non-exponential term in the rate expression for the reaction requires a highly special orientation of the reactants, while the normal frequency factor for the reverse reaction indicates that the geometry of the activated complex is similar to that of the adduct.[3(a),5] It is at once clear that the one-step mechanism is in harmony with these requirements, and scarcely less so

[4] A. Wassermann, *J. Chem. Soc.* 825, 1511 (1935); 432 (1936).
[5] C. Walling, *Free Radicals in Solution* Footnote, p. 188. Wiley, New York (1957).

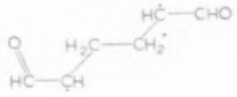
that the simple two-step mechanism is not. Since no conformational specificity is associated with the initial bond-forming process in the latter case, the requirement of similar geometry at the barrier and in the product is clearly violated, and further, it may be doubted that the frequency factor for the forward reaction should be as low as that observed.

THE EFFECTS OF SUBSTITUENTS

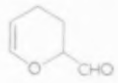
The attachment of groups of various kinds to any of the three unsaturated centers which take part in the Diels–Alder reaction exerts a marked effect upon the ease of the reaction, and upon its sense in unsymmetrical cases. Indeed, the reaction of a simple olefin with a diene takes place only with very great difficulty, and the olefinic components in those reactions which proceed smoothly and rapidly are invariably substances in which the reacting double bond is conjugated with one or more further unsaturated or equivalent groupings. Beyond that, the reaction is especially facilitated when the partners to the union are respectively laden with groups of opposite electrical character. It is easy to comprehend such influences on the basis of the two-step mechanism. For, the delocalization of electrons from each of the unsaturated systems which must be attendant upon the initial bond-forming process leaves on either side electrons which are relatively less stabilized through exchange with their former partners. Clearly, any group which stabilizes these partially freed electrons will facilitate the initial bond-forming process.

By contrast, the one-step mechanism seems ill-adapted to the rationalization of substitutive effects. Indeed, if two electrons from each partner must be simultaneously delocalized in order to participate in two simultaneous bond-forming processes, it might be expected that groups capable of conjugation would render reaction more difficult, in consequence of the demands which they would make upon the electrons necessary for bond formation in the reaction process.

Similarly, directive effects are much more clearly explicable in terms of the two-step mechanism. Thus, to choose an extreme example, it may not be doubted that the combination of two molecules of acrolein in a two-step process would lead initially to (XI),[2(c,g)] and thence to the observed product (XII). On the other hand, were the

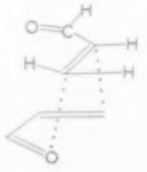


XI



XII

reaction to proceed through a one-step complex such as (XIII) or (XIV), it seems



XIII

XIV

highly probable that the polar forces within such complexes would operate in such wise as to render (XIII) more stable than (XIV).

NEW EVIDENCE

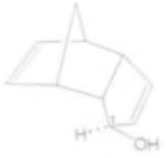
We turn now to new evidence which shows with special clarity that the thermal dissociation of di*cyclo*pentadiene derivatives takes place in two discrete and experimentally separable stages.

When *endo* di*cyclo*pentadiene (VI) is heated at 200°, it suffers a smooth reverse Diels–Alder reaction, with cleavage to two molecules of *cyclo*pentadiene.[6] The attachment of oxygen at C. 1 of the di*cyclo*pentadiene skeleton does not materially alter the course of the dissociation. When 1-acetoxydi*cyclo*pentadiene is heated at 200°, it is converted into *cyclo*pentadiene and acetoxy*cyclo*pentadiene. This demonstration is complicated by the lability of acetoxy*cyclo*pentadiene, but a simple proof of the course of the reaction is obtained when the decomposition is carried out in the presence of ethylene, which traps the cleavage products, respectively as bi*cyclo*heptene (XV) and 7-acetoxybi*cyclo*heptene (XVI).[7]

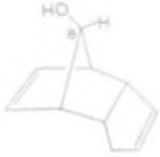
XV

XVI

In sharp contrast to the complete cleavages just described is the behavior of α-1-hydroxydi*cyclo*pentadiene (XVII)*[7(a,c),8] when it is heated to the relatively low



XVII



XVIII

temperature of 140°. Under these conditions, the alcohol is smoothly converted, in part, into an isomeric substance, which we have shown possesses the structure (XVIII). Thus, the new alcohol possesses the infrared bands at 3·28 μ, 6·18 μ and 6·37 μ, characteristic of the two double bonds of the di*cyclo*pentadiene system.[9] It forms a toluenesulfonyl derivative whose solvolysis is very sluggish,[10] and is reduced to a

* The prefix α is used arbitrarily to designate the isomer (XVII), while β designates the C. 1 epimer (*vide infra*). The configuration of the α alcohol at C. 1 has not previously been assigned, but follows from our observation that the new β compound is readily converted by very dilute hydrochloric acid in water/acetone to the α isomer. This conversion undoubtedly takes place under equilibrating conditions, and simple steric considerations leave no doubt that (XVII) must be the more stable of the two epimers.

[6] B. S. Khambata and A. Wassermann, *Nature, Lond.* **138**, 368 (1936); G. B. Kistiakowsky and W. H. Mears, *J. Amer. Chem. Soc.*, **58**, 1060 (1936); R. B. Moffett, *Organic Syntheses* Vol. 32, p. 41. Wiley, New York (1952).

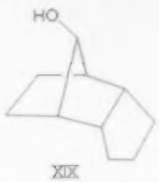
[7(a)] P. Wilder, Jr., Dissertation, Harvard (1950); [(b)] R. E. Vanelli, Dissertation, Harvard (1950); [(c)] C. J. Norton, Dissertation, Harvard (1955); [(d)] S. Winstein, M. Shatavsky, C. Norton and R. B. Woodward, *J. Amer. Chem. Soc.* **77**, 4183 (1955).

[8(a)] M. Rosenblum, *J. Amer. Chem. Soc.*, **79**, 3179 (1957); [(b)] K. Alder and F. H. Flock, *Chem. Ber.* **87**, 1916 (1954).

[9] P. von R. Schleyer, Dissertation, Harvard (1956); P. E. Fuchs, Dissertation, Harvard (1955); H. B. Henbest, G. D. Meakins, B. Nicholls and R. A. L. Wilson, *J. Chem. Soc.* 997 (1957).

[10] *Cf.* S. Winstein and E. T. Stafford, *J. Amer. Chem. Soc.* **79**, 505 (1957), who observed the relatively slow solvolysis of *syn*-7-norbornenyl toluenesulfonate.

tetrahydro derivative (XIX). The latter is oxidized to the corresponding ketone (XX),



XIX

XX

whose infrared spectrum possesses a carbonyl band of characteristic high frequency (5·65 μ),[7(c)] and which is reducible by the Wolff–Kishner method to the known *endo*tetrahydrodi*cyclo*pentadiene (XXI).[11]

XXI

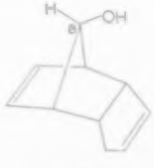
The conversion of α-1-hydroxydi*cyclo*pentadiene (XVII) into *syn*-8-hydroxydi*cyclo*pentadiene (XVIII) is an equilibrium reaction. When either alcohol is heated at 140°, it is converted into the same equilibrium mixture of (XVII) and (XVIII). The reaction is very smooth, it is accompanied by substantially no ancillary decomposition, and a careful search of the equilibration reaction mixtures reveals the presence of no substantial amounts of other isomers, or other products. The equilibrium constant for the reaction is approximately 1. Since the 8-alcohol is substantially more volatile than the 1-alcohol, the conversion of the latter into its isomer may be effectuated in almost quantitative yield by slow distillation.

Precisely similar phenomena are observed in the case of the new β-1-hydroxydi*cyclo*pentadiene (XXII) (see footnote p. 74), which is obtained by reduction of 1-ketodi*cyclo*pentadiene (XXIII)[8] by lithium aluminum hydride. When the β alcohol

XXII

XXIII

is heated at 140°, it too is converted into an isomeric substance, which in this case has been shown to be *anti*-8-hydroxydi*cyclo*pentadiene (XXIV). The new alcohol again possesses the characteristic infrared bands at 3·28 μ, 6·18 μ and 6·37 μ.[9] Its



XXIV

[11] J. Pirsch, *Chem. Ber.* **67**, 101 (1937).

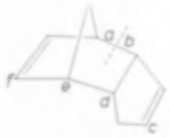
toluenesulfonyl derivative undergoes very ready solvolysis*[12] to give *anti*-8-acetoxydi*cyclo*pentadiene as sole product. It is reduced to a tetrahydro derivative, which is oxidized to the same 8-ketotetrahydrodi*cyclo*pentadiene (XX) which is obtained from the isomer (XIX). As in the case of the α isomer, the isomerization of the β alcohol (XXII) into *anti*-8-hydroxydi*cyclo*pentadiene (XXIV) is an exceptionally smooth reaction. Here again no secondary reactions of by-products are observed. In this case too, an equilibrium reaction is no doubt involved, but as would be expected on the basis of simple steric conditions, the equilibrium here lies strongly in favor of the 8-substituted alcohol (XXIV).

It is of particular significance that complete stereochemical integrity is maintained in both of the reactions just described. In the isomerization of 1-α-hydroxydi*cyclo*pentadiene only *syn*-8-hydroxydi*cyclo*pentadiene and no *anti*-8-hydroxydi*cyclo*pentadiene is formed. In the isomerization of 1-β-hydroxydi*cyclo*pentadiene, only *anti*-8-hydroxydi*cyclo*pentadiene and nc *syn*-8-hydroxydi*cyclo*pentadiene is produced.

How do these reactions proceed? We consider first, and reject at once, the possibility that the alcohol undergoes reversion of the Diels–Alder reaction, to give *cyclo*pentadiene and hydroxy*cyclo*pentadiene, which recombine to give the observed products. For, in that event, the observed stereochemical specificity of the reactions would be inexplicable. Lest an attempt be made to circumvent this argument with the proposal that the reversion does occur, and that the components are trapped in some kind of cage which ensures their recombination with approximate retention of the relevant original stereometrical relationships, we have converted the already very impressive stereochemical demonstration into a dramatic one. Thus, *the α and β alcohols*, (XVII *and* XXII), *were each resolved, and submitted to the isomerization reactions, with complete retention of optical integrity*. It would be a remarkable cage indeed which would permit to its captives the molecular motions required for the isomerization, while at the same time preventing those displacements which would lead to the symmetrical array (XXV), and thence to racemization.

XXV

It is now clear that the isomerizations which we have observed involve the scission of the bond *ab* of the di*cyclo*pentadiene skeleton (XXVI), and the constitution of a

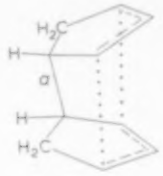


XXVI

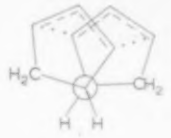
* Winstein *et al.*[12] observed the exceptionally rapid solvolysis of *anti*-7-norbornenyl toluenesulfonate. The difference in solvolytic behavior of the *syn* and *anti* 8-toluenesulfonyloxydi*cyclo*pentadienes is dramatic. The half-life of the *anti* compound in acetic acid at 25° is 8·45 min, while the *syn* isomer was unchanged under similar conditions for thirty days.

[12] S. Winstein, M. Shatavsky, C. Norton and R. B. Woodward, *J. Amer. Chem. Soc.* **77**, 4183 (1955); S. Winstein and M. Shatavsky, *Ibid.* **78**, 592 (1956).

new bond between *c* and *f*, while the integrity of the bond *de* is maintained. The molecules, in undergoing the transformation, must pass through a stage (XXVII≡ XXVIII), in which one bond is in process of formation while another is suffering



XXVII



XXVIII

cleavage.*[12]

We now know that cleavage of one bond of the di*cyclo*pentadiene molecule, with conversion to (XXVII), takes place relatively readily. We know further that if (XXVII) is more highly energized, a second bond, at *a*, breaks, and two molecules of *cyclo*pentadiene are produced. These facts lay the basis for presumption that in the *combination* of two molecules of *cyclo*pentadiene, (1) the rate-controlling process is the formation of a single bond between termini of the conjugated systems of the reacting molecules, and (2) after passage of the barrier, reaction proceeds to the same array (XXVII), and thence, with relatively facile formation of a second bond, to the product.

A NEW THEORY

We now generalize the conclusion of the preceding section, and propose that the Diels–Alder reaction takes place in the following way.

(1) The diene assumes, if it does not already have, the *quasi cis* conformation (XXIX).

XXIX

(2) The rate-controlling process consists in the formation of a single bond between one terminus of the diene system and one of the unsaturated centers of the olefin. Accordingly, the diene and the olefin approach one another initially in parallel planes, orthogonal to the direction of the bond about to be formed (cf. XXX-XXXI).

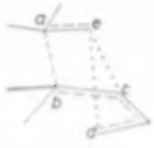
XXX

XXXI

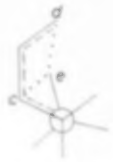
* The reaction is of course a special case of the Cope rearrangement.

[12] *Cf.* E. G. Foster, A. C. Cope and F. Daniels, *J. Amer. Chem. Soc.* **69**, 1893 (1947), and earlier papers.

(3) *Conformational specificity about the newly-forming bond is determined by secondary attractive forces involving the electrons not directly associated with the primary bonding process* (cf. XXXII≡XXXIII).* Thus, as electrons at *c*, *d* and *e* are

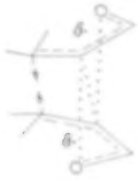


XXXII

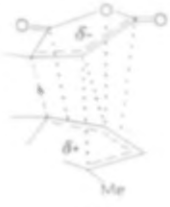


XXXIII

progressively freed of their involvement with their former partners at *a* and *b*, attractive electrostatic, electrodynamic, and even to some extent exchange forces (dotted lines *ed* and *ec* in XXXII≡XXXIII) stabilize the conformation shown as compared with other *a priori* available alternatives. It should be noted that by necessity the spins of all the electrons involved in these processes are appropriately coupled at all times. Conjugating substituents at *e*, *c* and *d* will be expected in general to facilitate reaction, through direct interaction with the mobile and partially freed electrons at the positions to which the groups are attached. Further, such groups will have the following important effects: (i) they will determine which termini of the reacting systems are involved in the primary bond-forming process; (ii) their specific nature will determine the extent to which the electronic displacements accompanying the primary bond formation are polarized; (iii) their mobile electrons will make additional contributions to the secondary attractive forces, and in that way determine which of the *a priori* possible orientations of diene with respect to olefin leads to the activated



XXXIV



XXXV

complex of lowest energy. All of these effects of substituents will become clear on scrutiny of the activated complexes for the dimerization of acrolein (XXXIV), and for the addition of maleic anhydride to piperylene (XXXV).

XXXVI

XXXVII

(4) After passage of the barrier, formation of the single bond at *ab* is first completed (cf. XXXVI), and the reaction proceeds to its conclusion with the relatively

* In this and subsequent formulae, solid lines represent σ bonds, broken lines symbolize partial bonds, and dotted lines delineate secondary attractive forces.

facile construction of a second full bond at *ed* (XXXVII). The latter process could be opposed by a further, relatively low, barrier, since the change involves substantial, though not great, geometrical displacements, and the attendant strains need not be fully compensated at all times by the stabilization accompanying the growth of the new bond. But it should be pointed out explicitly that we beg the question whether ours is a one-step or a two-step mechanism, that is, whether such a second, lesser barrier must be passed after traversal of the first. Certainly it is a *two-stage* mechanism, in that the formation of two bonds takes place in separable, even if overlapping, processes, discretely delineated in structural terms, and displaced in time. It is entirely possible, indeed likely, that a second, low barrier will be involved in some specific cases, and not in others. In any event, it must be emphasized that for virtually all predictive and explicative purposes, resolution of the extremely subtle problems associated with defining the precise topography of the energy surface for the reaction after passage of the first barrier is irrelevant.

In conclusion, we note that the theory of the Diels–Alder reaction here put forward possesses at one and the same time the divers favorable attributes which have hitherto been considered separately and exclusively characteristic of the one or the other of the previously proposed mechanisms. It shares with the two-step mechanisms the favorable predictive capacity in respect to the effects of substituent groups on ease and sense of reaction. Further, in common with the one-step mechanism, it readily accommodates the kinetic and thermodynamic evidence, since it assumes an activated complex which is relatively rigid, whose geometry is not markedly different from that of the product, and whose formation requires a highly special orientation of the reacting molecules. Finally, it is entirely in consonance with stereochemical observations, since the relative rigidity of the molecular species involved throughout reaction ensures that stereometrical relationships inherited from the reactants are maintained, and since, as compared with previous theories, it lends similar, but expanded physical meaning to the empirical principle of maximum accumulation of unsaturated centers.

EXPERIMENTAL

Melting points, unless otherwise stated, were taken in capillary tubes, and are corrected.

α-1-*Hydroxydi*cyclo*pentadiene* (XVII)

The alcohol was prepared according to the procedure of Rosenblum[8(a)] and Norton[7(c)] with some modifications. Freshly distilled di*cyclo*pentadiene (186 g) was dissolved in 500 ml dioxane in a one-liter three-necked flask equipped with a Hershberg stirrer and reflux condenser. Water (50 ml) and potassium dihydrogen phosphate (20 g) were added, and, while the solution was stirred and heated on a steam-bath, selenium dioxide (80 g, freshly prepared and sublimed[14]) was added. After 3 hr the mixture was cooled, the precipitated selenium was filtered immediately with suction, and the precipitate was washed with ether. The filtrate was shaken with 1 l. of saturated NaCl solution. The aqueous solution was drawn off and washed three times with 300 ml portions of ether. The combined organic solutions were then washed with 250 ml of 5 per cent aqueous sodium hydroxide and 500 ml of saturated

[14] N. Rabjohn, *Organic Reactions* Vol. V, p. 345. Wiley, New York (1949).

brine. The emulsion which formed was broken by filtration through Supercel. The organic phase was washed twice more with brine and dried over sodium sulfate. The solvent was removed at reduced pressure, and the residual oil was distilled (b.p. 67° at 0·1 mm) to yield 132 g (63%) of slightly yellow, waxy crystals. After redistillation this material was sufficiently pure for use in all the following experiments. The alcohol could be obtained by recrystallization from pentane as white crystals, m.p. 36·6–37·4°. It is reported by Rosenblum[8(a)] and Norton[7(c)] to be an oil and by Alder[8(b)] as a waxy mass, m.p. 40–50°.

A phenylurethan was prepared in the usual way; m.p. 139·6–140·0° (reported,[8(b)] m.p. 142°).

The thermal isomerization of α-1-*hydroxydi*cyclo*pentadiene* (XVII)

When the α alcohol is heated to a temp. in the neighborhood of 135–150°, a ready isomerization takes place. At temp. well below 135°, the isomerization does not occur noticeably. Thus, for example, refluxing the alcohol in benzene solution for two days results in no isomerization, and the starting material is recovered unchanged. Above 150°, cracking[8(a,b),15] and polymerization occur. That the isomerization is in fact an equilibration was demonstrated as follows. Pure α-1-hydroxydi*cyclo*pentadiene (162 mg) was placed in a Pyrex tube, which was then evacuated and sealed. Similarly, a sample of the pure *syn*-8-hydroxydi*cyclo*pentadiene (153 mg, *vide infra*) was sealed into an evacuated tube. The two tubes were placed in a round-bottomed flask partially filled with xylene and set for reflux. By refluxing the xylene around the tubes, a temp. of 138° was maintained for 6 hr. The tubes were then quickly cooled, opened, and the infrared spectra of the contents examined. The two samples had superimposable spectra, which, when compared with the spectra of known mixtures of the two alcohols indicated that this equilibrium mixture consists of 53 ± 5% *syn*-8-hydroxydi*cyclo*pentadiene and 47 ± 5% α-1-hydroxydi*cyclo*pentadiene.

Syn-8-*hydroxydi*cyclo*pentadiene* (XVIII)

α-1-Hydroxydi*cyclo*pentadiene was distilled slowly at a pressure of 35 mm through a jacketed distilling column (11·5 mm × 125 cm packed with ⅛ in. Pyrex glass helices). The still-pot was heated in an oil bath kept at 165–175°, and the column was maintained at 131–132°. The product which distilled (b.p. 126° at 35 mm) crystallized immediately, and precautions had to be taken to prevent its freezing in the still-head and fraction collector. The crude distillate consists almost entirely of *syn*-8-hydroxydi*cyclo*pentadiene contaminated with some of the starting material. The yield is limited only by the hold-up of the apparatus and by a very small amount of polymerization which occurs in the pot. If the same distilling column is used from one run to the next, the hold-up of the column no longer affects the yield. Typical results follow.

Fifty grams of the α-1-hydroxydi*cyclo*pentadiene were distilled through the column under the conditions described above. The distillate was collected in three fractions: the first, before the column was completely equilibrated, consisted of 6 g; the main fraction comprised 40 g; and a final few drops (ca. 1 g) were collected. Thus, the total recovery was 47 g (94%). The infrared spectra of the first two fractions were compared with the spectra of known mixtures of *syn*-8-hydroxydi*cyclo*pentadiene and

[15] K. Alder and F. H. Flock, *Chem. Ber.* **89**, 1732 (1956).

α-1-hydroxydi*cyclo*pentadiene, as well as with the spectra of *anti*-8-hydroxydi*cyclo*-pentadiene and di*cyclo*pentadiene. The absence of the latter two compounds, as well as ketonic material from cracking, was indicated by the absence of characteristic absorption (e.g., at 5·5–6·0 μ, 9·46 μ, 12·20 μ, 13·80 μ, 13·85 μ, 14·8 μ). In fact, the spectrum of the main fraction was identical with that of a mixture of 93% *syn*-8-hydroxydi*cyclo*pentadiene and 7% α-1-hydroxy*cyclo*pentadiene, while the spectrum of the fore-run was essentially identical with that of a mixture of 11% α-1-hydroxydi*cyclo*pentadiene and 89% *syn*-8-hydroxydi*cyclo*pentadiene.

The first fraction was recrystallized once from pentane, combined with the main fraction, and the combined products recrystallized three times more from pentane. This yielded 36·3 g (73%) of white crystals, m.p. 51·8–52·8°. A sample purified for analysis melted at 52·1–52·9°.

(Found: C, 80·95; H, 8·18; Calc. for $C_{10}H_{12}O$: C, 81·04; H, 8·16%).

The phenylurethan was prepared in the usual way and recrystallized from ligroin to constant melting point: m.p. 113·7–114·3°.

(Found: C, 76·39; H, 6·42; N, 5·06; Calc. for $C_{17}H_{17}O_2N$: C, 76·38; H, 6·41; N, 5·24%).

Oppenauer oxidation of syn-8-*hydroxydi*cyclo*pentadiene* (XVIII)

A solution of *syn*-8-hydroxydi*cyclo*pentadiene (509 mg) and quinone (607 mg) in 75 ml dry benzene was prepared in a 100 ml round-bottomed flask. After removing the last traces of water by distilling out a few milliliters of the solvent, aluminum *t*-butoxide (1 g) was added, and the mixture refluxed for 50 hr. The reaction mixture was cooled, acidified with dilute HCl, and filtered through Supercel. The aqueous phase was drawn off, and the organic phase washed twice with dilute HCl and four times with 5% NaOH. After the solution was dried over K_2CO_3, the solvent was removed at reduced pressure; 482 mg of oil was obtained, which crystallized on seeding with di*cyclo*pentadiene-1-one. The infrared spectrum of the product (300 mg) after two recrystallizations from petroleum ether was compared with that of authentic di*cyclo*pentadiene-1-one (XXIII).[8(a,b)] The two were in every respect identical. Further purification by recrystallization and sublimation afforded material, m.p. 65·3–65·6°; mixed with authentic di*cyclo*pentadiene-1-one (m.p. 65·2–65·6): m.p. 65·3–65·6°.

Tetrahydro-syn-8-*hydroxydi*cyclo*pentadiene* (XIX)

Syn-8-hydroxydi*cyclo*pentadiene (1·013 g) in absolute ethanol (5 ml) was hydrogenated at atmospheric pressure in the presence of 65 mg platinum oxide. 95% of the expected 2 moles of hydrogen was absorbed in 7 hr. The catalyst was filtered, the solvent removed *in vacuo*, and the residue sublimed at reduced pressure to yield 833 mg (80%) of white crystals, m.p. 109·5–109·9°.

On a larger scale, a solution of 20 g of *syn*-8-hydroxydi*cyclo*pentadiene in 200 ml of 95% ethanol was hydrogenated in the presence of 368 mg of platinum oxide in a shaker (initial pressure: 50 lo/in² above atmospheric pressure). After sublimation, 19·4 g (94%) of the tetrahydro derivative were obtained.

Purification was conveniently effected by recrystallization from ligroin. The analytically pure material melts at 110·5–111·5°.

(Found: C, 78·82; H, 10·66; Calc. for $C_{10}H_{16}O$: C, 78·89; H, 10·59%).

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Dicyclopentadiene-1-*one* (XXIII)

The ketone was prepared according to the procedure of Alder[8(b)] by chromic acid oxidation of α-1-hydroxydi*cyclo*pentadiene. The ketone was purified by recrystallization from ligroin and by sublimation at reduced pressure. The melting point was found to be 65·3–65·6° (reported: 80°[8(b)] and 59·0–59·5°[8(a)]). The 2,4-dinitrophenylhydrazone was prepared and recrystallized from aqueous ethanol, m.p. 199·2–199·5° (dec.) (reported,[8(a)] 203·5–204·0°).

β-1-*Hydroxydi*cyclo*pentadiene* (XXII)

To a stirred solution of lithium aluminum hydride (2·26 g) in anhydrous ether (1 l.) in a 2 l. three-necked flask, equipped with stirrer, condenser, and dropping funnel, a solution of 20·55 g of the above ketone (XXIII) in 200 ml ether was added slowly. The solution was stirred for 15 min after the addition was complete. It was then cooled and treated, with vigorous stirring, successively with 2·3 ml water, 2·3 ml 15% NaOH and 6·8 ml water.[16] The alumina was filtered and the ether removed *in vacuo*. The residue on recrystallization from a mixture of 50 ml ligroin and 150 ml pentane afforded 14·8 g (71%) of the alcohol. For analysis a sample was purified by recrystallization from pentane, from which the alcohol crystallizes as fluffy white needles, and sublimation at 0·05 mm pressure; m.p. 85·0–85·8°.

(Found: C, 81·20; H, 8·34; Calc. for $C_{10}H_{12}O$: C, 81·04: H, 8·16%).

Anti-8-*hydroxydi*cyclo*pentadiene* (XXIV)

A Pyrex bomb-tube partially filled with β-1-hydroxydi*cyclo*pentadiene (8·83 g) was evacuated and sealed. The tube was then placed in a round-bottomed flask and maintained at 135° for 22 hr by refluxing xylene around it. When cool, the tube was opened, and the contents transferred to a sublimation apparatus. The product was sublimed twice at reduced pressure, to yield 7·0 g (80%) of white, slightly oily crystals, which after two recrystallizations from pentane melted at 68·9–70·4°. A sample purified for analysis melted at 66·8–67·4°.

(Found: C, 81·08; H, 8·00; Calc. for $C_{10}H_{12}O$: C, 81·04; H, 8·16%).

The infrared spectrum of a sample of the crude material obtained by sublimation of the contents of the bomb-tube was compared with spectra of *syn*-8-hydroxydi*cyclo*pentadiene and β-1-hydroxydi*cyclo*pentadiene. The absence of these compounds from this material was witnessed by the lack of their characteristic absorption bands. For example, the following absorption bands present in the spectrum of the *syn*-8-ol: 14·10 μ, 14·45 μ, 12·94 μ, 12·81 μ, 9·76 μ, 9·68 μ, and of the β-1-ol: 13·11 μ, 12·82 μ, 11·06 μ, 9·84 μ, 9·70 μ were absent.

The phenylurethan was prepared and recrystallized from ligroin to a constant melting point, m.p. 136·2–136·5°.

(Found: C, 76·53; H, 6·64; N, 5·50; Calc. for $C_{17}H_{17}O_2N$: C, 76·38; H, 6·41; N, 5·24%).

Tetrahydro-anti-8-*hydroxydi*cyclo*pentadiene*

A solution of the above alcohol (XXIV, 931 mg) in absolute ethanol (10 ml) in the presence of 85 mg platinum oxide catalyst absorbed 97% of the theoretical two

[16] V. M. Micović and M. L. Mihailović, *J. Org. Chem.* **18**, 1190 (1953).

moles hydrogen at atmospheric pressure in less than 2 hr. The crystalline residue left after filtration of the catalyst and removal of the solvent *in vacuo* was recrystallized from ligroin to yield 750 mg (81%) of white crystals, m.p. 120·0–120·5°. Further recrystallization and sublimation at reduced pressure afforded the analytically pure material, m.p. 119·8–120·3°.

(Found: C, 78·91; H, 10·72; Calc. for $C_{10}H_{16}O$: C, 78·89; H, 10·59%).

*Tetrahydrodi*cyclo*pentadiene*-8-*one* (XX)

(a) *From tetrahydro*-syn-8-*hydroxydi*cyclo*pentadiene* (XIX). The alcohol (2·0 g) and freshly sublimed quinone (2·45 g) were dissolved in dry benzene (85 ml) in a 100 ml round-bottomed flask. To remove the last traces of water a few milliliters of benzene were distilled from the flask. Aluminum *t*-butoxide (4 g) was then added, and the mixture, protected from moisture, was refluxed for approximately 30 hr. After the flask had been cooled, the contents were poured into cold 5% HCl, and the aqueous layer drawn off. The benzene solution was washed once more with cold 5% HCl and three times with 5% NaOH, and then was dried over potassium carbonate. The solvent was distilled at reduced pressure, and the residue sublimed twice to yield 1·57 g (80%) of a slightly yellow camphoraceous product. Purification was effected by recrystallization from pentane. The analytically pure material consisted of colorless waxy crystals, m.p. 65° (Fisher–Johns block), which were too soft to place into a melting point tube.

(Found: C, 79·80; H, 9·48; Calc. for $C_{10}H_{14}O$: C, 79·95; H, 9·39%).

(b) *From tetrahydro*-anti-8-*hydroxydi*cyclo*pentadiene*. The latter (221 mg) and quinone (280 mg) in benzene solution (8 ml) was refluxed with aluminum *t*-butoxide (469 mg) for 40 hr. After the reaction mixture had been cooled and acidified with cold 5% HCl, insoluble material was removed by filtration through a mat of Supercel (which was then washed with pentane). The aqueous layer was drawn off, and the organic phase washed successively with cold water, cold 5% NaOH and cold water. After drying over sodium sulfate, the solvent was distilled at diminished pressure, and the residue sublimed to yield 128 mg (59%) of an oily solid. After purification, as above, by recrystallization from pentane and sublimation, its infrared spectrum was identical with that of the ketone prepared as in (a) (above).

Purified samples of the ketone prepared from the two epimers had identical melting points (65°, Fisher–Johns block) undepressed by admixture of the two. The infrared spectra of the two samples were superimposable. 2,4-Dinitrophenylhydrazones were prepared in the usual way from samples of the ketone prepared by the alternative methods, and these were recrystallized from aqueous ethanol to constant melting points, which follow:

2,4-DNP from tetrahydro-*syn*-8-hydroxydi*cyclo*pentadiene: m.p. 155·4–156·6°
2,4-DNP from tetrahydro-*anti*-8-hydroxydi*cyclo*pentadiene: m.p. 156·2–157·3°
mixed: m.p. 155·9–157·1°

The ultraviolet spectrum of the 2,4-dinitrophenylhydrazone was determined: λ_{max} (ethanol) 357 mμ (log $\varepsilon = 4{\cdot}4$).

*Wolff–Kishner reduction of tetrahydrodi*cyclo*pentadiene*-8-*one* (XX)

A solution of the ketone (587 mg) in triethylene glycol (20 ml) was treated with 0·4 ml 95% hydrazine. After the solution had been allowed to stand at room temp.

for 1 hr, benzene (45 ml) was added and water azeotroped from the reaction mixture over a period of 5 hr. KOH (2·5 g) was added, and water again was azeotroped from the mixture. Volatile materials were distilled, and the reaction flask, equipped with a short condenser leading to a fresh receiver, and thermometer extending into the reaction mixture, was heated to 205°. After 20 hr, the temp. was raised to distill out last traces of the reaction products. The distillate was diluted with its own volume of water and extracted twice with pentane. The pentane solutions, after being washed with 5% HCl, water, and 5% NaOH, were dried over K_2CO_3. The residual oil left after the solvent was distilled was freed of polar materials by elution from an alumina column (10 g, Woelm, activity I) with pentane. The eluted material was again placed on an alumina column (100 g, Woelm, activity I) and eluted with pentane. Sublimation of the crystalline residue left after removal of the solvent yielded 273 mg (51%) of the hydrocarbon. After one more chromatographic treatment and resublimation, the hydrocarbon was compared with authentic tetrahydrodi*cyclo*pentadiene.[11] Its melting point (74–76°) was identical with that of the authentic material and was undepressed on admixture with the latter. Its infrared spectrum, though lacking detail, was identical with that of the authentic sample.

Epimerization of β-1-*hydroxydi*cyclo*pentadiene* (XXII)

A mixture of β-1-hydroxydi*cyclo*pentadiene (570 mg) acetone (10 ml) and 30 ml 0·1 M HCl was stirred for 90 min at room temp. The solution was made basic by the addition of saturated K_2CO_3 solution, and 50 ml saturated NaCl solution were added. The mixture was extracted three times with 30 ml portions of pentane. The combined pentane/acetone solutions were washed once with brine and dried over sodium sulfate. The drying agent was filtered, and the solvent removed *in vacuo*, leaving 548 mg (96%) of an oil, the infrared spectrum of which was rich in detail and identical with that of α-1-hydroxydi*cyclo*pentadiene (XVII). The phenylurethan was prepared from this alcohol, and recrystallized twice from ligroin. Its melting point (140·0–140·1°) was undepressed by admixture with the phenylurethan of the alcohol produced by selenium dioxide oxidation of di*cyclo*pentadiene (m.p. 139·9–140·4°).

Syn-8-*tosyloxydi*cyclo*pentadiene*

Syn-8-hydroxydi*cyclo*pentadiene (6 g), dissolved in pyridine (16 ml) was treated with tosyl chloride (8·48 g). The flask was stoppered and shaken until all the solids had dissolved, and was allowed to stand at room temp. overnight.[17] The reaction mixture was poured into cold dilute HCl sufficient to neutralize all the pyridine. The precipitated solid was dissolved by the addition of benzene, and after the two phases were separated, the aqueous phase was extracted twice more with benzene. The combined benzene solutions were washed with dilute HCl and dilute NaOH, dried over K_2CO_3, and the solvent removed *in vacuo*. The tosylate is unstable to heat, and was recrystallized by dissolving it quickly in hot ligroin, cooling rapidly to room temperature, and finally cooling in an ice-bath. After two recrystallizations, 8·85 g (71%) of the tosylate were obtained. A sample purified for analysis melted at 96·4–96·8°.

(Found: C, 67·72; H, 6·08; Calc. for $C_{17}H_{18}SO_3$: C, 67·52; H, 6·00%).

[17] R. S. Tipson, *J. Org. Chem.* **9**, 235 (1944).

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Anti-8-*tosyloxydi*cyclo*pentadiene*

Anti-8-hydroxydi*cyclo*pentadiene (995 mg) was dissolved in 5·0 ml dry pyridine (freshly distilled from barium oxide), and the solution, in a 10 ml stoppered flask, was cooled in an ice/salt bath. Tosyl chloride (1·416 g, recrystallized from ether) was added, and the flask securely stoppered and shaken, with cooling, until solution was complete. The flask was then stored for 6 hr in the refrigerator (ca. 8°). The contents were poured into a cold solution of 1·65 ml of conc. H_2SO_4 in 50 ml water. The mixture was extracted three times with 30 ml portions cold benzene, and the combined benzene solutions were washed successively with cold 0·3 N H_2SO_4, cold water, cold 5% $NaHCO_3$, and cold water again. The benzene solution was dried over Na_2SO_4, and the solvent was carefully removed *in vacuo*. The residue was recrystallized by dissolving it in ca. 75 ml ligroin at room temp and cooling to Dry Ice temp. This afforded 1·10 g of white crystals. Concentration of the mother liquors at reduced pressure to half the original volume, and cooling yielded an additional 0·34 g, which after one more recrystallization from 15 ml of ligroin afforded 0·25 g of tosylate. The combined yield (1·35 g) is 66% of the theoretical. The tosylate is unstable at room temp. and above, and turns deep purple on warming. It can, however, be stored for weeks in a freezer.

(Found: C, 67·75; H, 6·06; Calc. for $C_{17}H_{18}SO_3$: C, 67·52; H, 6·00%).

Tetrahydro-syn-8-*tosyloxydi*cyclo*pentadiene*

A solution of tetrahydro-*syn*-8-hydroxydi*cyclo*pentadiene (XIX, 1·09 g) in pyridine (3 ml) was cooled in an ice-bath, and tosyl chloride (1·5 g) was added. The flask was stoppered and shaken to effect solution of the solids, and stored in the refrigerator for 2 hr and then overnight at room temp. The reaction mixture was treated with a cold solution of 2·5 ml conc. HCl in 20 ml water, and the product was then extracted twice with ether. The combined ether solutions were washed with dilute HCl, water, and 5% $NaHCO_3$, and then dried over Na_2SO_4. Removal of the solvent left an oil which crystallized on cooling and scratching. One crystallization from petroleum ether afforded 1·9 g of the tosylate, which after recrystallization melted at 46·5–46·8°.

Attempted acetolysis of tetrahydro-syn-8-*tosyloxydi*cyclo*pentadiene*

A solution of the tosylate (500 mg) potassium acetate (173 mg) in acetic acid (15 ml), sealed into an evacuated bomb-tube, was heated in a steam cone for 78 hr. The bomb was cooled, opened, and the contents diluted with water and extracted three times with chloroform. The combined chloroform solutions were washed successively twice with water and twice with $NaHCO_3$ solution, and dried over Na_2SO_4. Removal of the solvent left 485 mg (97% recovery) of the original tosylate, identified by its infrared spectrum, which was identical with that of the starting material.

Attempted acetolysis of syn-8-*tosyloxydi*cyclo*pentadiene*

A solution of 223 mg tosylate (m.p. 95·4–96·3°) and 102 mg potassium acetate in 10 ml acetic acid was allowed to stand at room temp. for 30 days. After dilution with 75 ml water, the mixture was extracted with four 30 ml portions of chloroform, and the combined chloroform solutions were washed successively with 5% NaOH and three times with water. After drying over Na_2SO_4 the solvent was distilled at reduced

pressure, leaving 220 mg (99% recovery) of slightly yellow crystals, m.p. 95·0–96·3°. The infrared spectra of the product and starting material were identical.

Acetolysis of anti-8-*tosyloxydi*cyclo*pentadiene*

(a) *Kinetics.* The rate of acetolysis at 25·03 ± ·02° of the tosylate in the presence of 0·1 M sodium acetate and 1% acetic anhydride was determined by the infinity titer method[18] as follows. The tosylate (294 mg) was weighed into a 10 ml volumetric flask, and the flask was then allowed to equilibrate with the thermostating bath. 10 ml of a solution of sodium acetate (0·1 M) in anhydrous acetic acid containing 1% excess acetic anhydride, previously equilibrated with the bath, were added to the tosylate, and the flask was shaken to effect solution. After about 4 min, the first 1·000 ml aliquot was withdrawn and reaction quenched by running it into petroleum ether in an ice-bath.[19] The amount of the petroleum ether used was varied in such a way that at the end-point of the titration the solution contained twice as much petroleum ether as acetic acid. Five drops of a saturated solution of bromphenol blue in acetic acid was added, and the sodium acetate titrated with 0·02 M perchloric acid in anhydrous acetic acid and 0·02 M sodium acetate in anhydrous acetic acid; excess perchloric acid was added and back-titrated with the sodium acetate solution to determine the titer, V, of the solution in milliliters of perchloric acid solution. A plot of ln $(V-V_\infty)$ against time was found to be a straight line with slope, $k = 1{\cdot}37 \times 10^{-3}$ sec^{-1}.

(b) *Product study.* A solution of 74 mg tosylate and 34 mg potassium acetate in 3·3 ml glacial acetic acid was allowed to stand at room temp. overnight. The reaction mixture was diluted with cold water and extracted three times with 15 ml portions of cold pentane. The combined pentane solutions were washed with cold water, cold 5% $NaHCO_3$, and cold water again. After drying over Na_2SO_4, the solvent was removed *in vacuo*, leaving 42 mg (91%) of an oil. Its infrared spectrum was compared with the spectra of the acetates (*vide infra*) of *syn*-8-hydroxydi*cyclo*pentadiene and *anti*-8-hydroxydi*cyclo*pentadiene. The infrared spectrum was identical with that of the *anti*-acetate. No evidence for the presence of the *syn* epimer could be found. Thus, there were no bands at 9·30 μ, 11·94 μ, 13·05 μ, 13·19 μ or 14·08 μ, all of which are present in the spectrum of the *syn*-acetate.

Anti-8-*acetoxydi*cyclo*pentadiene*

Anti-8-hydroxydi*cyclo*pentadiene (498 mg) was dissolved in pyridine (1·0 ml) and the solution cooled in an ice/salt bath. Acetic anhydride (1·1 ml) was added, and the mixture was swirled, stoppered, and allowed to stand at room temp. overnight. After 20 hr, the solution was poured into an ice-cold solution of 0·8 ml of conc. HCl in 20 ml water. The mixture was extracted with 3 ice-cold 20 ml portions of pentane, and the combined pentane solutions washed with cold 2% HCl, cold water, twice with cold 5% $NaHCO_3$, and again with cold water. After drying over Na_2SO_4, most of the pentane was removed at reduced pressure. In order to remove traces of polar impurities, the solution was put on a column of 10 g of Woelm alumina (activity I) and eluted successively with 50 ml portions each of pentane, 5% ether in pentane, and 25% ether in pentane. Removal of the solvents yielded 507 mg (80%) of the acetate,

[18] S. Winstein, C. Hanson and E. Grunwald, *J. Amer. Chem. Soc.* **70**, 812 (1948); S. Winstein, E. Grunwald and L. L. Ingraham, *Ibid.* **70**, 821 (1948).
[19] S. Winstein and D. Trifan, *J. Amer. Chem. Soc.* **74**, 1154 (1952).

a very pleasant-smelling oil. For analysis the product was re-chromatographed on alumina and distilled.

(Found: C, 75·80; H, 7·48; Calc. for $C_{12}H_{14}O_2$: C, 75·76; H, 7·42%).

Syn-8-*acetoxydi*cyclo*pentadiene*

Syn-8-hydroxydi*cyclo*pentadiene (3·75 g) in pyridine (6·0 ml) was treated with acetic anhydride (2·72 ml) and the flask swirled, stoppered, and allowed to remain at room temp. overnight. The reaction mixture was poured into an amount of dilute HCl calculated to neutralize the pyridine, and the product extracted three times with ether. The combined ether solutions were washed with dilute HCl, brine and 5% $NaHCO_3$. After drying over Na_2SO_4, the solvent was removed, and the residual oil was distilled at reduced pressure to yield 2·64 g of a pleasant-smelling oil, b.p. 83° at 0·6 mm. This was purified by chromatography on alumina and redistilled.

Resolution of α-1-*hydroxydi*cyclo*pentadiene* (XVII)

3-β-Acetoxy-Δ^5-etiocholenyl chloride was freshly prepared by allowing freshly recrystallized 3-β-acetoxy-Δ^5-etiocholenic acid* (36·9 g) and thionyl chloride (200 g) to react at room temp. for 4 hr. Removal of the excess thionyl chloride *in vacuo* yielded the crystalline acid chloride, which was dissolved in 300 ml dry pyridine (freshly distilled from barium oxide). The solution was then cooled in an ice-bath. The α-1-hydroxydi*cyclo*pentadiene (17·0 g) dissolved in 50 ml dry pyridine, was added. The flask was stoppered securely, shaken vigorously, and was then allowed to stand at room temp. overnight.

The cooled reaction mixture was poured into an ice-cold solution of 380 ml of conc. HCl in 2 l. of water. The mixture was shaken vigorously and filtered. The precipitate was washed with more cold dilute HCl and then with cold water to neutrality. Water was removed from the crude reaction product by drying *in vacuo* over calcium chloride. Yield: 47·0 g (94%).

The dried esters were dissolved in 2 l. of hot acetone. The solution was filtered and then concentrated to about 800 ml, at which point crystallization began. Cooling, followed by filtration, yielded 24·5 g of plates, m.p. 191–192·8°. After two more recrystallizations, the yield of the one pure diastereomer was 17·4 g (70%), m.p. 200·0–201·2°.

A sample prepared for analysis melted at 201·9–202·7°, and had $[\alpha]_D^{23}$ −110° ($CHCl_3$, c = 1·96).

(Found: C, 78·11; H, 8·46; Calc. for $C_{32}H_{42}O_5$: C, 78·33; H, 8·63%).

A suspension of this ester (17·2 g) in about 1800 ml anhydrous ether was slowly added, with vigorous stirring, to a suspension of lithium aluminum hydride (7 g) in 1200 ml anhydrous ether in a dry three-necked flask set for reflux. The reaction mixture was stirred for 30 min after addition was complete and was then cooled in an ice-bath. With vigorous stirring, 7 ml water were slowly added, followed by 7 ml 15% NaOH, and another 21 ml water. Stirring was stopped after another 5 min, and the reaction mixture filtered through a mat of Supercel. Ether was used to wash the precipitate. The combined solutions were transferred to a separatory funnel and washed twice with 200 ml portions water. Drying (Na_2SO_4), followed by removal of

* We wish to express our warm appreciation to Dr. Eugene P. Oliveto (Schering Corporation, Bloomfield), who kindly provided a generous sample of 3-β-acetoxy-Δ^5-etiocholenic acid.

the ether *in vacuo*, left a residue, which was shaken vigorously with approximately 1 l. of pentane. The steroidal alcohol was filtered, washed with more pentane, and the pentane largely removed from the filtrate. Cooling the concentrated solution precipitated the optically active α-1-hydroxydi*cyclo*pentadiene (3·68 g, 71%) as soft white crystals, m.p. 68–70·3°, $[\alpha]_D^{24}$ −87° ($CHCl_3$, $c = 2{\cdot}91$). The infrared spectrum (CS_2) of this material was superimposable in detail on that of the *dl*-α-1-hydroxydi*cyclo*pentadiene.

*Rearrangement of l-α-1-hydroxydi*cyclo*pentadiene* (XVII)

The optically active α alcohol (519 mg) was sealed into an evacuated Pyrex tube, which had been carefully cleaned to ensure a clean dry neutral surface. The sealed tube was heated in a bath of refluxing xylene (139–140)° for 6 hr. The tube was then quickly cooled and opened. The oily product had $[\alpha]_D^{25}$ −38° ($CHCl_3$, $c = 2{\cdot}21$). The components of the mixture were separated by chromatography on 50 g Florisil. The *syn*-8-hydroxydi*cyclo*pentadiene was eluted by ether/benzene (1:25) and was immediately followed by the α-1-hydroxydi*cyclo*pentadiene. Identical fractions were combined and sublimed, and mixed fractions were discarded.

The *syn*-8-hydroxydi*cyclo*pentadiene thus obtained (127 mg, white needles, m.p. 49·4–51·6°) had $[\alpha]_D^{22}$ +1·1°, $[\alpha]_{400\ m\mu}^{22}$ +32·9° ($CHCl_3$, $c = 9{\cdot}62$). Its infrared spectrum was identical with that of *dl-syn*-8-hydroxydi*cyclo*pentadiene. That the observed rotations were not due to the presence of a trace of the starting material (α-1-hydroxydi*cyclo*pentadiene) was demonstrated by a determination of the rotatory dispersion curve of the latter compound: $[\alpha]_D^{22}$ −86°, $[\alpha]_{400\ m\mu}^{22}$ −248° ($CHCl_3$, $c = 2{\cdot}21$). The rotations of the starting material and product are opposite in sign.

The recovered α-1-hydroxydi*cyclo*pentadiene had m.p. 69·2–70·9° and $[\alpha]_D^{23}$ −85° ($CHCl_3$, $c = 2{\cdot}21$).

*l-Di*cyclo*pentadienone*-1 (XXIII)

l-α-1-Hydroxydi*cyclo*pentadiene (2·35 g) was added to the complex formed from 4·45 g chromic anhydride and 45 ml dry pyridine, according to the procedure of Sarett.[20] After 24 hr at room temp., the mixture was poured into 400 ml water, and benzene was added. Insoluble material was removed by filtration. The layers were separated, and the aqueous phase re-extracted twice more with fresh portions of benzene, filtering as necessary. The combined benzene solutions (ca. 500 ml) were washed twice with water, twice with cold 20% HCl, and then three times with saturated brine to neutrality. The benzene was removed *in vacuo* after drying over potassium carbonate, leaving the crystalline ketone, which was recrystallized from ligroin: yield 1·93 g. After one more recrystallization from a small amount of ligroin, the yield was 1·90 g of white crystals, m.p. 72·6–76·4°. A small sample recrystallized from ligroin melted at 76·8–77·8°, and had $[\alpha]_D^{26}$ −162° ($CHCl_3$, $c = 3{\cdot}15$). Its infrared spectrum was identical with that of *dl*-di*cyclo*pentadienone-1.

*d-β-1-Hydroxydi*cyclo*pentadiene* (XXII)

In a dry three-necked flask, equipped with condenser, dropping funnel and stirrer, a suspension of 317 mg of lithium aluminum hydride in 150 ml dry ether was prepared. While stirring, a solution of the *l*-ketone (1·71 g) in 50 ml dry ether was added, and

[20] G. I. Poos, G. E. Arth, R. E. Beyler and L. H. Sarett, *J. Amer. Chem. Soc.* **75**, 422 (1953).

stirring was continued for another 15 min. The reaction mixture was cooled in an ice-bath, and, with vigorous stirring, 0·3 ml water, followed by 0·3 ml 15% NaOH and 0·9 ml water were added. The alumina was filtered through a mat of Supercel and washed with more ether. The combined ether filtrates were washed twice with water and dried (Na_2SO_4). After the removal of the solvent, the residue was twice recrystallized from ligroin and then sublimed: yield 1·09 g. The infrared spectrum of this product was extremely similar to, but not identical with, that of pure *β*-1-hydroxydi*cyclo*pentadiene. The product was therefore purified by chromatography on aluminum oxide (Merck). The alcohol was eluted with ether/pentane (1:1), and pure fractions were combined and sublimed. The pure product thus obtained had $[\alpha]_D^{25}$ +130° ($CHCl_3$, $c = 1{\cdot}82$) and melted at 83·7–84·8°. Its infrared spectrum (CS_2) was in every respect identical with that of *β*-1-hydroxydi*cyclo*pentadiene

*Rearrangement of d-β-1-hydroxydi*cyclo*pentadiene* (XXII)

The above alcohol (151 mg) was sealed into an evacuated clean dry Pyrex tube. The sealed tube was heated in a bath of refluxing xylene (140°) for 20 hr. It was then cooled and opened. The crystalline residue was scraped out and sublimed to yield 135 mg (90%) of white crystalline product, m.p. 65·5–67·6°, $[\alpha]_D^{25}$ +22·2° ($CHCl_3$, $c = 12{\cdot}4$). The infrared spectrum (CS_2) was compared with that of *dl-anti*-8-hydroxydi*cyclo*pentadiene. The spectra were superimposable.

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NOTES

Synthesis of fraxidin

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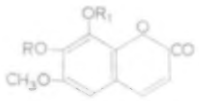
THE application[1] of Dakin's reaction to 7-methoxy-8-acetyl coumarin gives a satisfactory yield of 7-methoxy-8-hydroxy coumarin.

This method has been applied to the synthesis of fraxidin, a naturaliy occurring compound isolated by Späth and co-workers[2] from the bark of German ash wood and its constitution established as 6:7-dimethoxy-8-hydroxy coumarin (I). It was prepared by Wessley and Demmer[4] from fraxin, 6-methoxy-7-hydroxy-8-glucosidoxy coumarin by methylation and subsequent hydrolysis. Späth *et al.*[5] attempted the partial methylation of fraxetin (II) and obtained a mixture of the two monomethyl ethers (I) and (III) which was separated with difficulty. A satisfactory synthesis of fraxidin (I) has now been carried out using 6:7-dimethoxy-8-acetyl coumarin prepared by the method of Aghoramurty and Seshadri.[6] The identity of the final product was confirmed by the preparation of its methyl and ethyl ethers.



I R=CH_3; R_1=H
II R=R_1=H
III R=H; R_1=CH_3

EXPERIMENTAL

7-Methoxy-8-hydroxy coumarin. 7-Methoxy-8-acetyl coumarin[7] (2 g) was heated on a boiling water bath with aqueous sodium hydroxide (17 cc, 4%) for 15 min. The clear solution was cooled to 0° and hydrogen peroxide (1 cc, 30%) added during the course of 15 min. The mixture was left at 0° for 2 hr, acidified with dilute hydrochloric acid, extracted with ether and the ether evaporated. The residue was crystallised first from dilute methanol and finally from ethyl acetate as colourless rectangular prisms and needles, m.p. 172–73°, agreeing with the earlier record.[7] (Found: C, 62·2; H, 4·5; calc. for $C_{10}H_8O_4$: C, 62·5; H, 4·2%). On methylation with dimethyl sulphate and potassium carbonate in acetone solution it yielded 7:8-dimethoxy coumarin, m.p. 119–20°. Mixed m.p. with an authentic sample prepared by methylation of 7:8-dihydroxy coumarin[8] was undepressed. The same melting point was also recorded earlier.[9]

6:7-*Dimethoxy-8-hydroxy coumarin* (*fraxidin*) (I). 6:7-Dimethoxy-8-acetyl coumarin[6] (1 g) was dissolved in hot aqueous sodium hydroxide (10 cc, 4%), the solution cooled to 0° and treated slowly

[1] V. D. N. Sastri, N. Narasimhachari, P. Rajagopalan, T. R. Seshadri and T. R. Thiruvengadam, *Proc. Indian Acad. Sci.* **A37,** 681 (1953).
[2] D. B. Limaye and M. C. Joshi, *Rasayanam* 226 (1941).
[3] E. Späth and Z. Jerzmanowska Scienkiewiczowa, *Ber.* **B70,** 1019 (1937).
[4] F. Wessley and E. Demmer, *Ber.* **B62,** 120 (1929).
[5] E. Späth and Z. Jerzmanowska Scienkiewiczowa, *Ber.* **B70,** 1672 (1937).
[6] K. Aghoramurty and T. R. Seshadri, *J. Chem. Soc.* 3065 (1954).
[7] A. Gandini, *Gazz. Chim. Ital.* **70,** 611 (1940).
[8] V. Pechmann, *Ber.* **17,** 929 (1884).
[9] G. Bargellini, *Gazz. Chim. Ital.* **46,** 249 (1916).

with hydrogen peroxide (0·5 cc, 30%). After 2 hr at 0° it was acidified with dilute hydrochloric acid; the solid product (0·8 g) crystallised from methanol as colourless stout rectangular prisms, m.p. 196–97°. (Found: C, 59·5; H, 4·9; calc. for $C_{11}H_{10}O_5$: C, 59·5; H, 4·5%). Späth *et al.*[3] reported the same m.p.

Methylation with dimethyl sulphate and potassium carbonate in acetone solution gave 6:7:8-trimethoxy coumarin, m.p. 104–5°. Mixed m.p. with an authentic sample prepared by the methylation of 6-hydroxy-7:8-dimethoxy-coumarin with dimethyl sulphate and potassium carbonate in acetone medium was undepressed. Wessley and Demmer[10] reported same m.p. for this product.

The ethyl ether prepared by the ethylation of the above fraxidin sample crystallised from methanol as colourless fine needles, m.p. 108–9°, agreeing with fraxidin ethyl ether.[4]

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[10] F. Wessley and E. Demmer, *Ber.* **61**, 1279 (1928).

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Padmatin,* a new component of the heartwood of *Prunus puddum*

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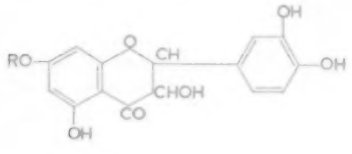
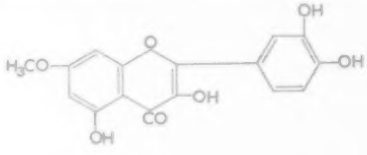
A new dihydroflavonol, Padmatin (Ib) has been isolated from the heartwood of *Prunus puddum*. A study of its reactions and properties indicates that it is 3:5:3′:4′-tetrahydroxy-7-methoxyflavanone and is related to taxifolin (Ia) since on methylation it gives taxifolin 5:7:3′:4′-tetramethylether. Oxidation of padmatin gives rhamnetin (II) which confirms the methoxy group in position 7.



Ia; R=H
Ib; R=CH_3



II

It has been recorded[1,2,3,4] that the components of the bark of *Prunus puddum* are 7-methyl ethers which resulted from the selective methylation of the corresponding hydroxy compounds which did not occur in the bark. The investigation of the heartwood has provided significant evidence in support of the suggestion because padmatin and its precursor taxifolin occur together in it. Another significant feature is the co-occurrence of taxifolin and its reduction product leucocyanidin in the wood.

EXPERIMENTAL

Extraction. Dry heartwood shavings (2 kg) were extracted (3 × 1 day) with cold light petroleum (b.p. 60–80°), the extract yielding on concentration a small amount of a wax, which gave no colour with alcoholic ferric chloride and with Mg and HCl. The residual heartwood was exhaustively extracted (6 × 12 hr) with boiling alcohol and the alcoholic solution concentrated to 300 cc under reduced pressure and excess of ether (3 l.) added. The mixture was kept in a refrigerator for one

* From the Indian plant Padmakashta. The investigation is Part VII of the series "Special components of commercial woods and related plant materia.I"

[1] N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.* **30A**, 271 (1949).
[2] N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.* **35A**, 202 (1952).
[3] B. Puri and T. R. Seshadri, *J. Sci. Industr. Res.* **13B**, 698 (1954).
[4] T. R. Seshadri, *Ann. Rev. Biochem.* **20**, 507 (1951).

month. The ether solution was separated from the sticky solid (fraction A), and concentrated to one litre, and extracted successively with 5% aqueous sodium carbonate (fraction B), 0·1% sodium hydroxide (fraction C) and 5% sodium hydroxide (fraction D). Complete evaporation of the remaining ether solution gave only a little wax.

Fraction A: (*leucocyanidin*). The sticky solid did not give a test for glycosides; after boiling with alcoholic sulphuric acid (7%), no test for sugars was obtained. Fraction A gave a test for leucocyanidin by the method already reported.[4]

Fraction B: (*taxifolin*. 1a). This fraction on acidifying with HCl deposited a dark product which solidified on cooling. It was filtered, washed with water and dried *in vacuo*. On dissolving in ethyl acetate (40 cc) and precipitating coloured impurities by adding light petroleum (b.p. 40–60°), the clear yellow solution on concentration gave a pale yellow solid (6·0 g) which on crystallisation from alcohol melted at 230–32°, and with ferric chloride in alcohol gave a brown colour, with Mg and HCl a red colour and with Zn and HCl a pink colour. Horizontal paper chromatography using phenol saturated with water gave Rf 0·78 at 33°. All these properties agreed with those of an authentic sample of +-taxifolin and the mixed melting point was undepressed. The identity was confirmed by oxidation[6] with iodine, glacial acetic acid and potassium acetate yielding quercetin and subsequently quercetin penta-acetate.

Fraction C: [*genkwanin, sakuranetin and padmatin* (1b)]. Addition of HCl gave a sticky solid which was washed with water, filtered and dried (*in vacuo*) (3·5 g). It was dissolved in boiling methanol (50 cc), and on cooling a yellow crystalline solid (0·4 g) was deposited which when recrystallised from ethanol melted at 282–83°, undepressed by an authentic sample of genkwanin. Its acetate (acetic anhydride-pyridine) melted at 194–95°.

The methanolic mother liquor was evaporated and the residue dissolved in ether, and the solution extracted with saturated aqueous borax solution. The remaining ether solution yielded on evaporation sakuranetin, which crystallised from ethanol as colourless prismatic needles (0·2 g) m.p. 151–52°. Its acetate[7] formed small colourless prisms from ethyl acetate, m.p. 98–99°.

The solid that separated on acidifying the borax extract was filtered, dried and crystallised from ethyl acetate-petroleum ether mixture when colourless needles of padmatin (1 g), m.p. 170–71° were obtained. An alcoholic solution gave a deep brown colour with ferric chloride, red with Mg and HCl and pink with Zn and HCl acid (Found: C, 59·9; H, 4·2; OMe, 9·2; $C_{16}H_{14}O_7$ requires: C, 60·4; H, 4·4; OMe, 9·7%).

Methylation of padmatin to taxifolin-tetramethyl ether. Padmatin (1b, 0·3 g), anhydrous potassium carbonate (2·5 g), dry acetone (20 cc) and dimethyl sulphate (2 cc) were refluxed for 15 hr. The product crystallised from alcohol as colourless needles, m.p. 169–70° undepressed by an authentic sample of taxifolin tetramethyl ether.[8]

Iodine oxidation of padmatin to rhamnetin (II). Padmatin (1b, 0·5 g) was dissolved in glacial acetic acid (15 cc) and fused potassium acetate (2·5 g) added. Iodine (0·4 g) in glacial acetic acid (10 cc) was added to the boiling solution during the course of an hour and heating continued for another hour. Acetic acid was removed under reduced pressure and saturated sulphur dioxide water (150 cc) added. The solid obtained was filtered, washed with water and dried (*in vacuo*). It was first crystallised from ethylacetate-petroleum ether mixture and then from alcohol yielding yellow needles (0·2 g), m.p. 290–92° alone or when mixed with an authentic sample of rhamnetin. Circular paper chromatography using phenol saturated with water as solvent at 30° gave Rf 0·80, while butanol-acetic acid-water gave Rf 0·88. These properties and colour reaction, agreed with those of rhamnetin prepared by Jain *et al.*[5] Acetylation (acetic anhydride, pyridine) gave colourless needles of rhamnetin tetraacetate m.p. 186–87°; mixed m.p. with an authentic sample was undepressed. The infra-red spectra of the above product and an authentic sample of rhamnetin (solid in potassium bromide) showed peaks at 3·1(s), 6·2, 6·4(s), 6·7, 6·9(w), 7·5(w), 7·6(s), 8·1, 8·3, 8·6, 9·2(w), 9·7(w), 10·1, 10·5(w), 10·7(w), 11·4(w), 12·2, 12·7(w)μ.

Fraction D: (*sakuranetin and prunetin*). The extract was acidified with HCl and the precipitate was dried, refluxed with benzene (100 cc) and the solution filtered and concentrated to (40 cc). On cooling it deposited a colourless crystalline solid which on recrystallisation from ethanol gave

[4] R. Robinson and G. M. Robinson, *Biochem. J.* **27**, 206 (1933).
[5] V. B. Mahesh and T. R. Seshadri, *Proc. Indian Acad. Sci.* **41A**, 220 (1955).
[6] N. Narasimhachari and T. R. Seshadri, *Proc. Indian Acad. Sci.* **30A**, 274 (1949).
[7] A. C. Jain, K. S. Pankajamani and T. R. Seshadri, *J. Sci. Industr.* **12B**, 127 (1953).
[8] F. E. Kurth, *J. Org. Chem.* **21**, 304 (1956).

colourless prismatic needles (2·0 g) m.p. 151–52°. The product agreed in all its properties and colour reaction with sakuranetin. Its acetate prepared by the procedure of Narasimhachari *et al.*[7] gave small colourless prisms, m.p. 98–99°.

The benzene insoluble portion gave on crystallisation from alcohol pale yellow needles (1 g) m.p. 236–38°, undepressed by prunetin and acetylation yielded colourless needles, m.p. 222–24° undepressed by prunetinacetate.

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The preparation of nitroanthraquinones by the peracetic acid oxidation of aminoanthraquinones

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Some time ago, in connection with other work, the need arose for quantities of 1-chloro-2-nitroanthraquinone. This compound had been prepared previously in 36 per cent crude yield[1] from 2-amino-1-chloroanthraquinone via the diazonium sulfate, and in unspecified yield[2] by persulfuric acid oxidation of the amine. However, we were induced to consider the use of peracetic acid for this oxidation by a report[3] of the simple conversion, in this manner, of 1:2-diaminoanthraquinone into 1-amino-2-nitroanthraquinone.

The reaction proved to be so convenient and efficient that the preparation of other nitroanthraquinones was examined. Nine amino-anthraquinones were thus converted into their nitro homologs in yields ranging from 35–82 per cent. The best yields (61–82 per cent) were encountered in the oxidation of simple aminohaloanthraquinones. The presence of negative groups adjacent to the amino group appears beneficial, since 2:6-diamino-1:5-dichloroanthraquinone and 1:4-diamino-2:3-dichloroanthraquinone were successfully oxidized, while the corresponding unchlorinated diamines gave only mixtures of unidentified products.

Kopetschni reported[2] 1-amino-4-chloroanthraquinone to be oxidized only to the nitroso homolog by the action of persulfuric acid. Peracetic acid oxidation, however, readily produced 1-chloro-4-nitro-anthraquinone. Oxidation of 1:2-diaminoanthraquinone produced, as reported,[3] some 1-amino-2-nitroanthraquinone provided the reaction mixture was heated only briefly. Continued heating, however, gave mixtures of unidentified products, in which, to judge from the yellow color, the 1-amino group was no longer present.

The reaction of 1:4-diamino-2:3-dichloroanthraquinone was unique in that only one of the amino groups suffered oxidation. Heating the product with fresh peracetic acid produced no further oxidation. On the other hand, the introduction of two nitro groups into the same ring appears to be no obstacle, since 2:3-dinitroanthraquinone was obtained from 2-amino-3-nitroanthraquinone.

Recently, Emmons described[4] his careful work upon the peracetic acid oxidation of simple amines to nitro homologs, and indicated that inferior results were obtained in the case of weakly basic or negatively substituted amines. Our results appear to contradict this generalization (as amines of the anthraquinone series are very weakly basic), and are more in agreement with the results obtained[5] by using peroxytrifluoro-acetic acid as the oxidant. It is possible that the use of the latter reagent would give superior yields in the oxidation of aminoanthraquinones, but this was not investigated.

EXPERIMENTAL

General procedure. Commercial 40% peracetic acid and a product of similar strength prepared[3] by admixture of 30% hydrogen peroxide, acetic anhydride and acetic acid, were used interchangeably.

[1] W. Bradley and E. Leete, *J. Chem. Soc.* 2129 (1951).
[2] E. Kopetschni, *Ger. Pat.* 363,930; *Frdl.* **14**, 850 (1926).
[3] I. G. Farbenindustrie, A. G., *P.B. Report No.* 70341, frames 14040-2.
[4] W. D. Emmons, *J. Amer. Chem. Soc.* **79**, 5528 (1957).
[5] W. D. Emmons, *J. Amer. Chem. Soc.* **76**, 3470 (1954).

All melting points were taken in Pyrex capillaries using a Hershberg melting point apparatus and Anschütz thermometers.

TABLE 1. NITROANTHRAQUINONES FROM THE OXIDATION OF AMINOANTHRAQUINONES

Aminoanthraquinones	Nitroanthraquinones	Yield (%)	m.p. (°C)		Analyses C	H	Cl	N	O
2-Amino-1-chloro-	1-Chloro-2-nitro-	82	264·4–266·3[a]	Calc.:	58·42	2·11	12·33	4·87	22·27
				Found:	—	—	—	—	—
1-Amino-2-chloro-	2-Chloro-1-nitro-[b]	75	282–284[c]	Found:	58·42	2·10	12·60	5·22	—
1-Amino-4-chloro-	1-Chloro-4-nitro-[d]	73	257·0–258·5[e]	Found:	58·91	2·10	12·28	4·43	22·18
2-Amino-3-bromo-	2-Bromo-3-nitro-	61	281·5–283·1[f]	Calc.:	50·60	1·81	24·10[g]	4·21	19·28
				Found:	50·80	1·88	24·20	4·27	19·10
2:6-Diamino-1:5-dichloro-	1:5-Dichloro-2:6-dinitro-	52	346·0–347·5[h]	Calc.:	45·78	1·10	19·34	7·63	26·15
				Found:	45·75	1·37	18·97	8·04	25·65
1-Amino-5-nitro-	1:5-Dinitro-	62	>360[i]	Calc.:	56·40	2·02	—	9·39	32·20
				Found:	56·43	1·84	—	9·47	—
1-Amino-8-nitro-	1:8-Dinitro-	38	315–322d[j]	Found:	56·30	1·93	—	9·61	32·23
2-Amino-3-nitro-[k]	2:3-Dinitro-	36	276–277[l]	Found:	56·42	2·08	—	9·36	—
1:4-Diamino-2:3-dichloro-	1-Amino-2:3-dichloro-4-nitro-	35	328·4–330·5[m]	Calc.:	49·85	1·78	21·05	8·32	19·00
				Found:	50·42	1·86	21·01	8·23	18·74

[a] Yellow irregular platelets, crystallized once from acetic acid. Lit.,[1,2] m.p. 262–263°; 257–258°.

[b] Previously prepared[3] in 11·8 per cent yield by nitration of 2-chloroanthraquinone.

[c] Ochre needles, crystallized three times from acetic acid. Lit.,[1] m.p. 280–281°.

[d] Previously prepared[4] in 30 per cent yield by nitration of 1-chloroanthraquinone.

[e] Orange needles, twice crystallized from acetic acid. Lit.,[4] m.p. 259°.

[f] Yellow platelets, twice crystallized from benzene and once from chlorobenzene.

[g] Bromine analysis.

[h] Yellow platelets, crystallized three times from acetic acid.

[i] Tan microcrystals from glycol diacetate. Lit.,[5] m.p. 385°.

[j] Golden prisms, three times crystallized from chlorobenzene. Lit.,[5] m.p. 312°.

[k] Prepared by tosylamidation of 2-bromo-3-nitroanthraquinone, followed by hydrolysis.

[l] Golden-tan platelets, twice crystallized from chlorobenzene and twice from glycol diacetate.

[m] Brown microneedles, crystallized three times from chlorobenzene and once from glycol diacetate.

[1] A. Eckert and K. Steiner, *Monatsh.* **35**, 1129 (1914).

[2] E. Hefti, *Helv. Chim. Acta* **14**, 1404 (1931).

The amines employed were purified samples of commerically available vat dye intermediates. The aminoanthraquinone was mixed with the peracetic acid (20 ml/g amine) and the mixture was heated to the boiling point for ½–½ hr. When larger (>10 g) quantities of amine were used, the peracetic acid was diluted with an equal volume of glacial acetic acid to moderate the reaction. The cooled solution was drowned, and the nitroanthraquinone was filtered and crystallized. The products are listed in Table 1, and the yields are those of the purified products.

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2-Benziminazolylmethyl*iso*thiouronium salts

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The recent publication[1] of a preparation of 2-benziminazolylmethyl*iso*thiouronium hydrochloride prompts us to report an examination of this compound which we carried out some time ago as an alternative to benzyl*iso*thiouronium hydrochloride for the characterisation of carboxylic acids. It was thought that the associating properties of the benziminazole ring system might lead to carboxylic acid salts with higher melting points than those of the benzyl analogs, and that the difference in melting point between neighbouring members of homologous series might be increased. A few salts of the more volatile carboxylic acids were prepared by metathesis from the hydrochloride; they showed similar solubility characteristics and melting points which are compared in Table 1. Basification of solutions of 2-benziminazolylmethyl*iso*thiouronium hydrochloride in air produced a colourless, odourless solid, m.p. 184–186°c; which is probably the corresponding disulphoxide (Found: N, 15·9, calc. for $C_{16}H_{14}O_2N_4S_2$: N, 15·65%). Hughes and Lions[2] reported its melting point as 182°; the corresponding mercaptan melted at 158°. Thus, the only advantage that might be claimed over the use of the well established benzyl*iso*thiouronium hydrochloride was the freedom from the nauseating smell of benzyl mercaptan frequently associated with its use, and so the investigation was not continued. The fact that the melting points of benzyl- and 2-benziminazolylmethyl*iso*thiouronium salts are in the main so close together supports the view[3] that the nature of the radicals attached to the thiourea and to the carboxyl group make little or no contribution to the stability of the crystal. Walker based this conclusion on a comparison of the melting points of benzyl and substituted benzyl*iso*thiouronium salts and some additional support is now available from a system containing a markedly different heterocyclic structure attached to the thiourea group.

Table 1. 2-Benziminazolylmethyl*iso*thiouronium salts

Acid	M.p.	Formula	Nitrogen Calc.	Found
Trifluoroacetic	167°	$C_{11}H_{11}O_2N_4F_2S$	17·5	18·0
Formic	154° (152°)	$C_{10}H_{12}O_2N_4S$	22·2	21·9
Acetic	150° (136°)	$C_{11}H_{14}O_2N_4S$	21·1	21·3
n-Butyric	151·5° (150°)	$C_{13}H_{18}O_2N_4S$	19·1	19·0

Figures in parentheses indicates m.p.s of corresponding benzyl analogs.[4]

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[1] A. I. Misra, *J. Org. Chem.* **23**, 897 (1958).
[2] G. K. Hughes and F. Lions, *J. Proc. Roy. Soc., N.S.W.* **71**, 209 (1938).
[3] J. Walker, *J. Chem. Soc.* 1996 (1949).
[4] J. Berger, *Acta Chem. Scand.* **8**, 427 (1954).

The polymerisation of epoxides by metal halide catalysts

(*Received* 18 *October* 1958)

At the Nottingham Conference on High Polymers (July, 1958) Professor G. Gee and his colleagues[1] advanced a mechanism for the polymerisation of propylene oxide in the presence of ferric chloride which included both (a) a cationic mechanism using carbonium ions terminally, and in a distinct second stage (b) a complex-formation and migration mechanism.

(a) $FeCl_3 + CH_2(O)CHMe \longrightarrow Cl_3Fe^-\text{—}O\text{—}CH_2\text{·}\overset{+}{C}HMe$

which $+ n\,CH_2(O)CHMe$

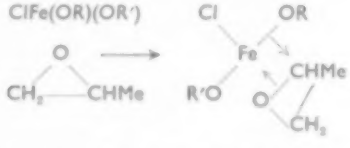
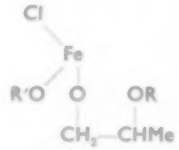
$Cl_3Fe(O\text{—}CH_2\text{—}CHMe)_n\text{—}O\text{·}CH_2\overset{+}{C}HMe$

with termination by formation of $Cl_2Fe(O\text{·}CH_2\text{·}CHMe)_n\text{·}O\text{·}CH_2\text{·}CHMeCl$

A second similar process affords $ClFe(OR)(OR')$

where $R = (O\text{·}CH_2CHMe)_xCl$

and $R' = R$ or is $(O\text{·}CH_2\text{·}CHMe)_{x+y}Cl$

(b) $ClFe(OR)(OR') \longrightarrow$  $\longrightarrow$ 

As the product remains of the form $ClFe(OR)_2$ the process can be continued with formation of a high polymer.

This latter idea amounts to insertion of the polymerising unit between the metal atom and the first oxygen atom of the chain. It is fully analogous to Professor C. E. H. Bawn's view[2] of the formation of polymethylene and substituted polymethylene chains from diazoalkanes and trivalent boron catalysts, and also to the present writer's conception of the formation of polyethylene using Ziegler catalysts.[3] It seems, however, unnecessary to postulate a different type of mechanism as in (a); the complex migration process of (b) may be used from the beginning and throughout the sequence of reactions. The assumption must be made that the migratory aptitude of –OR is superior to that of –Cl and also that the latter decreases in the series Cl_3Fe, Cl_2Fe, ClFe. This is in complete agreement with Bawn's conclusion that all the products from BF_3 and nCH_2N_2 are $F_3B(CH_2)_nF$.

The first product is then $Cl_2Fe\text{·}O\text{·}CH_2\text{·}CHMeCl$ and this is rapidly changed by further union with C_3H_6O and OR migration to $Cl_2Fe(OCH_2\text{·}CHMe)_xCl$ (where x is a small number). At this stage the slower Cl from Cl_2Fe attacks the complexing unit and we get

$$Cl.Fe(OCH_2CHMe)_xCl$$
$$|$$
$$OCH_2.CH\ Me\ Cl$$

There can be little doubt but that when the metal carries *two* chains the rate of complex formation will be drastically reduced; transition from Fe–O– to –O–Fe–O could have a similar effect. Naturally the shorter chain could include more than one $–O–C_2$ unit, in fact just as many as are needed to produce the steric hindrance contemplated. Probably only one group, as above, would suffice. It may be anticipated, therefore, that the two chains produced in the first rapid phase of the polymerisation will not be even approximately equal in length.

[1] *Technical Press reports*, e.g. R. O. Colclough, E. Gee, W. C. E. Higginson, S. B. Jackson and M. Litt; *Plastics* October (1958).
[2] Communication to the Nottingham Conference on High Polymer Technology, July (1958).
[3] R. Robinson, *The Chemical Age* May 5th (1956); lecture to joint meeting of the Italian Chemical Society and the Society of Chemical Industry, Turin, Nov (1957). (In the press).

The writer's interest in what may be thought a point of minor importance is mainly that he sees no necessity for the assumption of fully developed carbonium ions as intermediates in reactions. The processes so illustrated in terms of current dogma, can always be considered as concerted and the cationic charge can be dissipated before it reaches its maximum possible value.

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The reductive coupling of triphenylchlorosilane: evidence for the triphenylsilyl Grignard reagent*

(*Received* 27 *October* 1958)

WE wish to report a new reaction in organosilicon chemistry, the coupling of two molecules of a chlorosilane by a Grignard reagent to produce the Si–Si linkage. The nature of the reaction products indicates that probably an organosilylmagnesium compound is formed as an intermediate. This intermediate would constitute the first known example of a "silyl Grignard reagent".

When 0·05 mole of triphenylchlorosilane was refluxed for 18 hours or longer with 0·10 mole of *cyclo*hexylmagnesium bromide in 250 ml of tetrahydrofuran, hexaphenyldisilane, m.p. 365–366°, was produced in 67 per cent yield. One mole each of *cyclo*hexene and *cyclo*hexane are produced for each mole of $Ph_3SiSiPh_3$ formed in this coupling reaction. Phenyl and 2-methyl*cyclo*hexyl Grignard reagents gave 51 per cent and 62 per cent yields respectively of $Ph_3SiSiPh_3$ under the same conditions. The solvent has an important influence on the course of the reaction since no disilane is obtained when tetrahydrofuran is replaced by the less basic solvent diethyl ether.

The nature of the reaction suggests that a silylmetallic intermediate may be involved. Indeed, other investigators have shown that organosilylmetallic compounds R_3SiM (M = Na, K, Li) will couple with chlorosilanes to produce the Si–Si linkage,[1,2] and Gilman has noted the stabilization of R_2SiM compounds by tetrahydrofuran.[2,3,4] The most significant evidence in favor of the organosilylmagnesium intermediate in our reaction comes from experiments using trimethyl chlorosilane. Me_3SiCl is not coupled by *cyclo*hexylmagnesium bromide in refluxing tetrahydrofuran, and after 24 hours most of the Me_3SiCl so treated can be recovered unchanged. However when a mixture of Ph_3SiCl and Me_3SiCl was treated with the same Grignard reagent system, *$Ph_3SiSiMe_3$, m.p.* 106–108°, *was produced in* 14 *per cent yield.* It is difficult to account for the formation of this unsymmetrical coupling product except by the reaction of the intermediate Ph_3SiMgX with Me_3SiCl. Apparently aromatic groups on silicon are necessary for the stabilization of the silyl Grignard reagent, just as they appear necessary for the formation of organosilylalkali compounds.[4]

We suggest the following tentative mechanism for the coupling reaction with *cyclo*hexyl Grignard reagent. Ph_3SiCl and *cyclo*hexylmagnesium bromide may undergo a four-center reaction, with the formation of $Ph_3SiMgBr$, *cyclo*hexene, and HCl:

The $Ph_3SiMgBr$, which need not be present in large concentration at any time, would couple with an additional molecule of chlorosilane. The HCl formed as a by-product would attack another molecule

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of *cyclo*hexylmagnesium bromide, accounting for the formation of *cyclo*hexane. This mechanism is consistent with additional experiments which show that (a) reduction of Ph_3SiCl to Ph_3SiH is not a part of the coupling reaction, and (b) the coupling reaction proceeds by a polar, rather than a free-radical, mechanism. Further studies of the limitations and uses of the coupling reaction are in progress.

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Asymmetric annellation effects

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Successive connexion of two diphenylene systems (rings 1, 2 and 3, 4 respectively) to benzene forming triphenylene II and tetrabenzanthracene III respectively causes very different spectral shifts.

$$\lambda_\beta = 1819 \xrightarrow{+751} 2570 \xrightarrow{+355} 2925\ \text{Å}$$

$$\sqrt{\lambda_\beta} = 42{\cdot}65 \xrightarrow{+8{\cdot}05} 50{\cdot}70 \xrightarrow{+3{\cdot}40} 54{\cdot}10\ \sqrt{\text{Å}}$$

I II III

This is in striking contrast to the constant shifts in the acene and phene series (linearly and angularly condensed benzene rings respectively)[2] and it is incompatible with the resonance theories about aromatic character which would require a symmetric annellation effect.

The above shifts for the β-bands are recorded in wavelength (Å) and in $\sqrt{\text{Å}}$, the latter being a scale for reciprocal nuclear charges. The nature of this electronic asymmetry becomes obvious if the second shift is deducted from the β-band of triphenylene II. This means the elimination of the influence of the two angular rings (1 and 2) in II. The result is a β-band at 2237 Å which is almost identical with β-band found in the absorption spectrum of naphthalene which is at 2210 Å for alcoholic solution. It is obvious that the first annellation with rings 1 and 2 produces an induced benzenoid ring in "Bz" and extends the aromatic system of the central benzene ring to a naphthalene system, whilst the second annellation with ring 3 and 4 does not extend it to an anthracene system but forms an empty ring "E".

It appears that the formation of an induced π-electron sextet in the ring "Bz" has preference over a symmetric distribution of π-electrons as required by the resonance theory. It is also a new manifestation of the Robinson aromatic sextet in its original definition. Since no aromatic sextet is formed in ring "E" it must be concluded that each inherent benzenoid ring (as marked by the circles) can transfer two π-electrons only to the induced benzenoid ring (Bz).

This asymmetric annellation effect can also be observed in higher tetrabenzacenes, dibenzacenes and in the perylene series.

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Perylene-3:9-quinone

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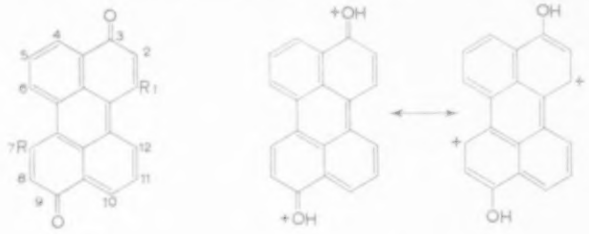
THE chemistry of extended quinones has been little studied owing possibly to the difficulty of their preparation in quantity. Todd and co-workers examined the properties of perylene-3:10-quinone[1] and 4:9-dihydroxyperylene-3:10-quinone[2] as an aspect of the chemical studies of aphid pigments; the properties of perylene-3:9-quinone, (I, R = H), have been examined in an analogous manner.

Perylene-3:9-quinone has been prepared by a new method, namely the oxidation with iodine in pyridine of 3:9-diketo-1:2:3:7:8:9-hexahydroperylene,[3] the overall yield from anthracene being 40 per cent. Oxidation with chromic oxide in sulphuric acid gives anthraquinone-1:5-dicarboxylic acid[4] identified as its methylester;[5] reductive acetylation gives 3:9 diacetoxyperylene. Perylene-3:9-quinone reacts readily with piperidine and *cyclo*hexylamine at 90° in presence of air to give dipiperidino and di*cyclo*hexylamino derivatives, both of which are hygroscopic. With alkali a dihydroxy derivative is probably formed but this could only be isolated as its dihydrotetracetyl derivative. This disubstitution with nucleophilic reagents contrasts with the monosubstitution of perylene-3:10-quinone where steric factors prohibit the attack of a second substituent.[1]

Quinone addition must occur on the 1:2 and 7:8 double bonds because of their relative stabilisation in the molecule and assuming normal addition as in perylene-3:10-quinone the substituents must be orientated at positions 1 and 7, (I, R = $-NC_5H_{10}$, or $-NC_6H_{11}$). This is borne out by the infra-red data, thus perylene-3:9-quinone has its carbonyl absorption at 1664 cm^{-1}—indicating less effective conjugation than other extended quinones—and those of its diamino derivatives at c.a. 1620 cm^{-1}. This lowering is due to the changed electron distribution in the carbonyl bonds under the influence of the electron repelling amino groups[6] at 1 and 7.



I II

Perylene-3:9-quinone shows a bathychromic shift in its light absorption on change of solvent from chloroform to sulphuric acid and this is due to the contribution of the new electronic forms (II etc.), following protonation of the carbonyl groups. The spectra of the diamino derivatives is unchanged on similar treatment, the electron attracting $-\overset{+}{N}H-$ groups inhibit the mesomeric shifts leading to structures such as II, and also therefore protonation of the carbonyl groups.

EXPERIMENTAL

Since several of the compounds described do not have m.p., identification is based upon analysis and infra-red spectra.

Perylene-3:9-quinone. 3:9-Diketo-1:2:3:7:8:9-hexahydroperylene (1·0 g) was dissolved by warming in pyridine (25 cc) and then cooled to 10°. Addition of an ice cold solution of iodine in pyridine (0·5 g in 10 cc), gave a precipitate of perylene-3:9-quinone (0·9 g) which was filtered off after an hour. The quinone was purified in portions by extraction into chloroform in a soxhlet apparatus, evaporation to a small bulk (5 cc) and addition of hot methanol (20 cc); on standing overnight the quinone

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separated in fine black needles showing a violet reflex, m.p. >350°. Material dried at 120°/0·05 mm for 20 hr (Found: C, 84·8, H, 3·3; Calc. for $C_{20}H_{10}O_2$: C, 85·1, H, 3·6%). *Perylene*-3:9-*quinone* was sparingly soluble in organic solvents giving claret coloured solutions, in conc H_2SO_4 the solution was bichromatic appearing blue by direct and red by reflected light. Light absorption in $CHCl_3$: max at 244, 276, 427, 529, and 570 mμ; log ε 4·35, 4·90, 4·23, 4·64 and 4·78 respectively; min at 253, 325, 446, and 546 mμ; log ε 4·20, 3·45, 3·81, 4·33 respectively; inflexion at 365 mμ; log ε 3·84. Light absorption in conc H_2SO_4: max at 263, 292, 447, 575, and 636 mμ; log ε 4·72, 4·43, 4·45, 4·53 and 4·68 respectively; min at 279, 345–346, 485, and 596 mμ; log ε 4·37, 3·62, 4·21, and 4·37 respectively. The infra-red spectrum (KBr disk) showed max at 1098, 1149, 1193, 1212, 1271, 1306, 1354, 1395, 1455, 1545, 1597, 1664, and 2902 cm^{-1}.

3:9-*Diacetoxyperylene*. Perylene-3:9-quinone (250 mg), sodium acetate (30 mg), zinc dust (750 mg) and acetic anhydride (25 cc) were refluxed for 3 hr. The solution was filtered whilst still hot and the residue washed with acetic anhydride (10 cc); the combined washings and filtrate on cooling gave 3:9-*diacetoxyperylene* (150 mg). The product recrystallised as fine yellow needles from the same solvent, m.p. 272–273°. (Found: C, 77·9; H, 4·2; $C_{24}H_{16}O_4$ requires: C, 78·2; H, 4·4%). The compound dissolved in chloroform gave a yellow solution with a blue fluorescence. Light absorption in $CHCl_3$: max at 253, 396, 416, and 446 mμ; log ε 4·40, 4·16, 4·45, and 4·52 respectively; min at 318, 399, and 426 mμ; log ε 3·92, 4·12, and 4·25 respectively. The infra-red spectrum (KBr disk) showed a max at 1760 cm^{-1}.

1:7 *Dicyclohexylaminoperylene*-3:9-*quinone*. Finely powdered perylene-3:9-quinone (200 mg) was heated on a steam bath at 90° with pyridine (25 cc) and *cyclo*hexylamine (15 cc) for 36 hr when the solution was a deep brown colour. The solvents were removed under reduced pressure, the residue dissolved in chloroform (25 cc) and filtered free of insoluble material. Concentration of the chloroform solution and addition of hot methanol (15 cc) gave on cooling 1:7-*dicyclohexylaminoperylene*-3:9-*quinone* (170 mg) as small black needles. The compound was recrystallised from chloroform–methanol, m.p. >350°. (Found: 77·3, 77·4, H, 6·7, 6·4, N, 5·3; Calc. for $C_{32}H_{32}O_2N_2.H_2O$: C, 77·7, H, 6·9, N, 5·7%). After drying material at 110°/0·05 mm for 24 hr: (Found: C, 80·4, H, 6·5; Calc. for $C_{32}H_{32}O_2N_2$: C, 80·7; H, 6·7%). Light absorption in $CHCl_3$: max at 296, 455, and 481 mμ; log ε 4·92, 4·46, and 4·50 respectively; min at 374 and 462 mμ; log ε 4·32 and 4·45 respectively; inflexions at 430–435 and 472–474 mμ; log ε 4·39 and 4·48. Light absorption in conc H_2SO_4: max at 256 and 487 mμ; log ε 4·96 and 4·63; min at 394 mμ; log ε 4·34. Infra-red spectrum (KBr disk) showed max at 762, 821, 837, 886, 904, 927, 982, 1030, 1102, 1146, 1182, 1234, 1250, 1341, 1360, 1400, 1510, 1580, 1598, 1622, 2820, and 2880 cm^{-1}.

1:7-*Dipiperidinoperylene*-3:9-*quinone*. Perylene-3:9-quinone (150 mg) was heated for 6 hr at 90° with pyridine (5 cc) and redistilled piperidine (10 cc), at which stage the solution was a deep red colour. The residue on removal of the solvents under reduced pressure was dissolved in chloroform and filtered. Concentration of the chloroform and addition of hot methanol (20 cc) precipitated the product (100 mg) on cooling. 1:7-*Dipiperidinoperylene*-3:9-*quinone* crystallised as a black microcrystalline powder with a brown reflex from pyridine–methanol, m.p. >350°. (Found: C, 71·2, 71·6, H, 6·4, 6·6, N, 5·3; Calc. for $C_{30}H_{28}O_2N_2.3H_2O$: C, 71·7, H, 6·8, N, 5·67%). Material dried at 120°/0·03 mm for 30 hr (Found: C, 80·1, H, 6·3, N, 6·2; $C_{30}H_{28}O_2N_2$ requires: C, 80·4, H, 6·2, N, 6·2%). Solutions of the compound in organic solvents were pale red. Light absorption on $CHCl_3$: max at 251, 385, 404, 482, and 496 mμ; log ε 4·90, 4·48, 4·46, 4·50, and 4·50 respectively; min at 379, 395, 422, and 490 mμ; log ε 4·46, 4·44, 4·44, and 4·46. Light absorption in conc H_2SO_4: max at 270, 471, and 489 mμ; log ε 4·66, 4·48, and 4·48 respectively; min at 392 and 482 mμ; log ε 4·35 and 4·45. Infra-red spectrum (KBr disk) showed max at 805, 842, 1024, 1061, 1106, 1131, 1151, 1225, 1242, 1410, 1430, 1510, 1578, 1600, 1621, 2810, 2875 cm^{-1}.

1:3:7:9-*Tetra-acetoxyperylene*. A suspension of finely powdered perylene-3:9-quinone (600 mg) in dioxan (200 cc) containing sodium hydroxide (200 cc; 10%) was refluxed for 12 hr when the solution was a deep red. The solution was filtered and reduced to 50 cc bulk on a rotary evaporator, cooling to 0° overnight gave a black precipitate of the sodium salt which was filtered free and washed with water. The sodium salt was dissolved by boiling in 50 per cent aqueous ethanol, filtered and acidified with dil H_2SO_4. The hydroxyquinone separated as a black amorphous solid (150 mg), but was not amenable to recrystallisation because of its insolubility. Its solution in conc H_2SO_4 was violet in colour.

The crude hydroxy–quinone (150 mg) was boiled under reflux with acetic anhydride (50 cc),

sodium acetate (25 mg) and zinc dust (750 mg) for 4 hr and the filtered solution poured into sodium acetate solution (2 N). After 1 hr the latter solution was extracted with chloroform (2 × 50 cc) and the chloroform extracts washed with sodium bicarbonate solution and water. Evaporation of the solvent gave a brown gum which was dissolved in benzene (5 cc) and absorbed on a column of precipitated silica (12 × 4 cm, in benzene) and the yellow orange band eluted with further benzene (350 cc). Evaporation of the benzene gave a light orange solid which crystallised from acetic anhydride as an orange powder (15 mg) m.p. 245–250° (d). (Found: C, 69·8, H, 4·4; Calc. for $C_{28}H_{20}O_4$: C, 69·4, H, 4·1%). Light absorption in $CHCl_3$: max at 396, 421, and 450 mμ; log ε 4·15, 4·40, and 4·51 respectively; min at 404 and 432 mμ; log ε 4·13 and 4·23.

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Electron transference in the attack of atoms or radicals upon carbon-hydrogen bonds

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PROF. J. KENNER has recently discussed a number of reactions wherein carbon-hydrogen bonds are broken and alkyl free radicals thereby generated.[1] His interpretation is that this process should always be formulated as involving two or more steps with electron transference being the dominant and initial process.

$$R{-}H + X\cdot \longrightarrow R{\cdot}\overset{+}{H}\ X{:}^- \longrightarrow R\cdot + H{-}X$$

Although I agree in principle to the importance of electron transference in the reactions of atoms and radicals having a high electron affinity, I believe the details of the process have been incorrectly interpreted by Prof. Kenner. It is my belief that electron transference should be considered as a stabilizing factor in the transition state rather than the demanded reaction path.[2]

TRANSITION STATE

$$R{-}H + X\cdot \longrightarrow \Big[\underset{\text{I}}{R{:}H\,X\cdot} \leftrightarrow \underset{\text{II}}{R^+H{\cdot}X{:}^-} \leftrightarrow \underset{\text{III}}{R{\cdot}H{-}\ X{:}^-}\Big] \longrightarrow R\cdot + H{-}X$$

In terms of complete electron transference it is difficult to see why the relative reactivities of nuclear substituted toluenes or cumenes toward a free radical or atom should be dependent upon the structure of the radical or atom.

$$Y{-}C_6H_4{-}CH_3 + X\cdot \xrightarrow{k_x} Y{-}C_6H_4{-}CH_2\cdot + HX$$

According to the Kenner postulate the polar effect (the effect of the polar nature of Y on k_x) in the reactions of atoms and radicals which have a high electron affinity (e.g. Cl·, Br·) or a low electron affinity (e.g. CCl_3·) should be equivalent. In actual fact an appreciable polar effect is observed for chlorine and bromine atoms (k_x is reduced by electron-withdrawing substituents) whereas no polar effect has been detected in the reactions of trichloromethyl radicals.[3] In terms of resonance stabilization of the transition state these facts can be rationalized easily since the contribution of structure II should be most important when X· has the highest electron affinity.

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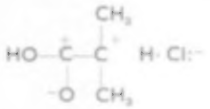
In terms of complete electron transference it would be expected that all atoms or radicals would remove the same hydrogen atom from a substrate containing a number of different carbon-hydrogen bonds. This is definitely not in accord with experimental observations.[4] For example, methyl radicals and chlorine atoms differ considerably in their point of attack on *iso*butyric acid. Methyl radicals attack the weakest carbon–hydrogen bond of the molecule to yield the 3°-alkyl radical predominately[5] whereas chlorine atoms attack mainly the β-hydrogen atoms.[6]

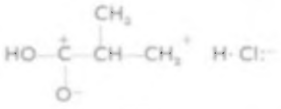
$$CH_3\cdot + (CH_3)_2CHCO_2H \longrightarrow CH_4 + (CH_3)_2\dot{C}CO_2H$$

$$Cl\cdot + (CH_3)_2CHCO_2H \longrightarrow HCl + \cdot CH_2CH(CH_3)CO_2H$$

In terms of the stabilization of the transition state, resonance structure II would be expected to be more important for the chlorine atom than for the methyl radical because of the relative electron affinities of these species.[7] Thus abstraction of a hydrogen atom by a methyl radical proceeds *via* a transition state resembling III and product stability controls the point of attack. Stabilization of the transition state by II is not important because of the low electron affinity of the methyl radical. On the other hand the chlorine atom which has an extremely high electron affinity attacks the β-carbon–hydrogen bond of *iso*butyric acid, the bond having the highest electron density. The transition state for the attack of a chlorine atom upon the β-carbon–hydrogen bond can be stabilized by electron transference (II-β) whereas the transition state for attack at the α-carbon–hydrogen bond would not be expected to be stabilized by electron transference because of the unfavorable adjacent charge in II-α.



II-α



II-β

Evidence for II as a contributing structure to the transition state for hydrogen abstraction has been furnished by the correlation of the relative reactivities of toluene and cumene derivatives toward various electrophilic atoms and radicals by means of Brown's σ^+-parameters.[8]

The finding of a linear free energy relationship between the rates of hydrogen abstraction from *meta- and para*-substituted toluenes and cumenes and the rates of hydrolysis of *meta- and para*-substituted dimethylbenzyl chlorides[9] suggests that both reactions involve transition states possessing similar stabilization. The similarity of resonance structure II for hydrogen abstraction and the transition state for the hydrolysis of dimethylbenzyl chlorides is apparent.

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Papers to be published in future issues

G. W. K. Cavill, P. S. Clezy, J. R. Tetaz and R. L. Werner: The chemistry of mould metabolites—III. Structure of cinnabarin (polystictin).

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F. KORTE, J. FALBE und A. ZSCHOCKE: α-Hydroxyalkyliden-lacton-Umlagerung—IX. Synthese des D,L-Iridomyrmecins und verwandter bicyclischer Lactone.

K. J. CLARK, G. I. FRAY, R. H. JAEGER and Sir ROBERT ROBINSON: Synthesis of D- and L-*iso*iridomyrmecin and related compounds.

A. H. BECKETT, N. J. HARPER, A. D. J. BOLON and T. H. E. WATTS: Stereochemistry of the reduction of tropinone.

G. A. RASUWAJEW, L. M. BOBINOWA und V. S. ETLIS: Gewinnung und Eigenschaften einiger titanorganischer Verbindungen.

T. L. V. ULBRICHT: Syntheses of pyrimidine-lithium compounds.

N. R. AYYANGAR, B. S. JOSHI and K. VENKATARAMAN: Anthraquinone and anthrone series—XXIII. The non-identity of 1:3:8-trihydroxy-2-hydroxymethylanthraquinone with versicolorin and a synthesis of damnacanthol and damnacanthal.

IMPORTANT EDITORIAL ANNOUNCEMENT

TETRAHEDRON LETTERS

to be published fortnightly as a rapid medium for the publication of communications in organic chemistry in preliminary form

ORGANIC chemists, like other scientists, have felt the need for reliable media in which to announce, with a minimum of delay, their more significant findings in a preliminary form. In highly competitive fields of investigation it has been fruitful to publish a novel advance, once its broad nature was clear, in condensed form in order to establish priority and the right to elaborate details for fuller publication at comparative leisure. In addition, all investigators, reflecting the high degree of enthusiasm and interest with which they regard their work, have a natural desire to share the excitement of new developments. For these reasons, the preliminary communication has long played a valuable part in the dissemination of scientific information.

Both the main purposes are best served at the international level and by as rapid a means of publication as possible. Following the lead of the American Physical Society in establishing the fortnightly *Physical Review Letters*, the Board of Editors of *Tetrahedron* have accepted the offer of Captain I. R. MAXWELL, Publisher at Pergamon Press, to separate the publication of articles and preliminary communications. *Tetrahedron* will continue to appear monthly as the international journal for major contributions to organic chemistry, while *Tetrahedron Letters* will appear fortnightly as the international medium for the publication of urgent communications. Offered at no extra cost to individual subscribers to *Tetrahedron*—who certify that copies are for their personal use—and at £7 ($20) post paid (air mail charges extra), to libraries, Government Departments and industrial establishments, *Tetrahedron Letters*, to be printed by the most modern techniques, will publish acceptable, well-prepared letters within two to sixteen days of receipt at the Publishing Office.

Letters may announce experimental or theoretical results of organic chemical interest which are considered to be novel and significant. They may also be of a critical or speculative nature, and in that event will be assessed for their positive value and degree of originality. Every effort will be made to ensure editorial consideration with respect to acceptability within two days of receipt. Letters from the American continent should be addressed to Professor W. DOERING (Department of Chemistry, Yale University, New Haven, Connecticut) and from the rest of the world directly to "Tetrahedron Letters", Pergamon Press Ltd., 4 Fitzroy Square, London W.1.

Notes in so far as they report fragmentary results of lesser significance will no longer be accepted by the Editors of *Tetrahedron* and its *Letters*. *Tetrahedron Letters* will publish immediately after acceptance, the abstracts of papers to appear in *Tetrahedron* (this is in addition to the preliminary communications) unless countermanded beforehand by the responsible author.

Helpful instructions for authors in the preparation of preliminary manuscripts for production in *Tetrahedron Letters* can be supplied free of charge upon request at any Pergamon Press Office.

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FOREWORD

FOR some years it has been the policy of the Chemistry Department of Indiana University to hold occasional conferences on timely subjects in specialized fields of chemistry. It is hoped that these meetings of specialists from diverse parts of the United States and abroad render a service to the advancement of science. The first such conference, in 1951, was on "Organic Sulfur Chemistry". Its success prompted the organization of a second conference held in 1954 on "Coordination Compounds". It is perhaps symptomatic of the trends in modern science that the subject of the most recent conference, "Hyperconjugation", represents probably an even narrower field of specialization than those of the first two.

The possibility of C–H electron delocalization as a means of explaining the effects of certain alkyl substituents on reaction rates was first suggested by J. W. Baker and W. S. Nathan in 1935. In 1941 R. S. Mulliken, C. A. Rieke and W. G. Brown published a quantum theoretical consideration of C–H electron delocalization with particular reference to ground state and spectroscopically excited states and introduced the term "hyperconjugation" to refer to this effect. The term met with quick general acceptance and has since been used, perhaps rather loosely with at least in some cases an implied meaning which was not envisaged by these authors. Many results from spectroscopic, thermochemical, molecular dimensional and reaction kinetic observations have been presented in the literature and interpreted with reference to hyperconjugation. A certain degree of self-consistency has been achieved in the interpretation of data in each of the different fields. However, the development of a unified picture of hyperconjugation has been plagued by apparent mutual inconsistencies in the ideas derived from the several different areas. As an example of this, the so-called "Baker–Nathan Order" of electron-releasing effects of alkyl groups ($Me > Et > Pr^i > Bu^t$) in reaction kinetic and equilibrium data has been considered to be indicative of important hyperconjugative interaction between the group and an electron-deficient center. But such orders are generally not characteristic of spectroscopic, thermochemical or molecular dimensional data where hyperconjugation has nevertheless been thought to be important. This introduces the problem of C–C electron delocalization or C–C hyperconjugation which has been suggested by several authors but never examined from a quantum theoretical view. These and other problems combined with the diverse nature of the evidences pertaining to hyperconjugation seemed to make the topic an ideal one for the type of conference which we at Indiana University like to sponsor.

The Conference on Hyperconjugation was held at Indiana University 2–4 June, 1958. The total registration was 117, including 61 participants from 23 states other than Indiana and 3 from the United Kingdom.

The conference heard the sixteen scheduled major papers as well as the results of several important investigations presented by participants from the floor during discussion sessions. The discussions were lively and, as befits a growing vital science, at times controversial. Considerable discussion evolved around Professor Dewar's idea

that conjugation as well as hyperconjugation is unimportant in "classical" molecules such as butadiene or propene. Other high points in the discussions centered on the appropriateness of linear free energy equations in treating hyperconjugation, the usefulness of various theoretical models in hyperconjugation calculations, the roles of carbon–carbon vs. carbon–hydrogen hyperconjugation, conformation influences on hyperconjugation and the rather small but persistent Baker–Nathan orders observed in reactivity studies. A number of participants seriously questioned the existence of important hyperconjugation effects and offered alternative explanations of some of the relevant data. It seemed agreed that the Baker–Nathan order usually involves very small effects and may well have an origin different from that which accounts for the much larger discrepancy between the electron-releasing abilities of hydrogen and the alkyl groups.

The Indiana University Foundation and the Department of Chemistry who organized the Conference gratefully acknowledge the generous financial support of the National Science Foundation, the American Cyanamid Co., the Eli Lilly Co., the Humble Oil and Refining Co., the Monsanto Chemical Co., the Shell Development Co. and the Standard Oil Co. of Indiana. We are also grateful to the editors and publisher of *Tetrahedron* for this publication of the conference papers. Finally, we would like to express our indebtedness to the authors of the papers presented at the conference and published in this volume for so generously and unselfishly contributing their time and efforts in providing the real substance of the conference. Any success which was achieved is in the last analysis due to their efforts and imagination.

V. J. Shiner, Jr.
E. Campaigne
Conference Co-chairmen

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AN ASSESSMENT OF SOME EXPERIMENTAL APPROACHES TO NH AND OH HYPERCONJUGATION

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IT is well known that the first experimental indications which were interpreted as showing that alkyl groups could release electrons conjugatively to attached unsaturated systems were those discussed by Baker and Nathan,[1] and depended on the observation that, whereas inductive electron release should be in the order Me < Et < Pr^i < Bu^t, the order of electron release observed in suitable cases involved reversals towards the order Me > Et > Pr^i > Bu^t. Many clear-cut examples are now established, and this aspect of the subject does not need further elaboration here.

Evidence for C–H *hyperconjugation in electrophilic aromatic substitution*

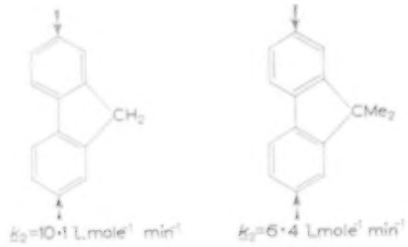
Aromatic substitutions are classically those reactions from which the theories of electronic displacements have been most extensively documented. Hyperconjugation would be expected to show up in such substitutions, since they are considerably facilitated by electron release, particularly of a conjugative character. Nitration seems to be an exception here; the inductive order has been observed for *para* substitution.[2] But since it was shown that in molecular bromination the methyl group is superior to the *tert.*-butyl group in promoting reactivity,[3, 4, 5] a number of similar examples have been substantiated in full experimental detail. Some of these will be discussed below. A case in which we have been interested is the bromination, by positive brominating agents, of alkylbenzenes in aqueous dioxan. The following results were obtained:[6]

The results illustrate confirmation that the inductive effect dominates the reactivity sequence at the *meta* position, as has been illustrated by other workers also.[7]

[1] J. W. Baker and W. S. Nathan, *J. Chem. Soc.* 1844 (1935).
[2] H. Cohn, E. D. Hughes, M. H. Jones and M. Peeling, *Nature, Lond.* **169**, 291 (1952).
[3] P. B. D. de la Mare and P. W. Robertson, *J. Chem. Soc.* 279 (1943).
[4] P. W. Robertson, P. B. D. de la Mare and B. E. Swedlund, *J. Chem. Soc.* 782 (1953).
[5] E. Berliner and F. J. Bondhus, *J. Amer. Chem. Soc.* **68**, 2355 (1946); E. Berliner and F. Berliner, *Ibid.* **71**, 1195 (1949).
[6] P. B. D. de la Mare and J. T. Harvey, *J. Chem. Soc.* 36 (1956); *Ibid.* 131 (1957).
[7] E. Berliner, F. Berliner and I. Nelidow, *J. Amer. Chem. Soc.* **76**, 507 (1954); E. Berliner and F. Berliner, *Ibid.* **76**, 6179 (1954).

Two further examples are given; they involve chlorinations in acetic acid. The first was studied in part by us, but in full experimental detail by Brown and his co-workers.[8] For the partial rate factors given below we have used his isomeric proportions and our value[3] for the relative reactivities:

The second has been examined only in part; it is the comparison of the relative rates of chlorination in acetic acid of fluorene and 9:9-dimethylfluorene.[9]



Since fluorene is known to give almost exclusively the 2- and 2:7'-chloro derivatives,[10] the sequence is established for 2-substitution as being in the hyperconjugation order; in this example, hyperconjugation in its conventional description involves an extended conjugated system, of the type illustrated in formula (I).

I

C–C *hyperconjugation*

It has seemed reasonable intuitively that the C–H bond should be better capable of conjugative electron release than the C–C bond. There seems to be nothing, however, in the theories of hyperconjugation to indicate that C–C hyperconjugation could be completely neglected. Although C–C hyperconjugation has been considered theoretically by various workers, Berliner and Bondhus[11] were probably the first writers to apply to a specific chemical example the theory that the *tert.*-butyl group has an accelerating power determined considerably by C–C hyperconjugation. It

[8] H. C. Brown and L. M. Stock, *J. Amer. Chem. Soc.* **79**, 5175 (1957); and personal communication.
[9] P. B. D. de la Mare, D. M. Hall, M. M. Harris and M. Hassan, *Chem. & Ind.* 1086 (1958).
[10] J. Buffle, *Helv. Chim. Acta* **15**, 1483 (1932).
[11] E. Berliner and F. J. Bondhus, *J. Amer. Chem. Soc.* **70**, 854 (1948).

was held that the reactivity of *tert.*-butylbenzene in molecular bromination was too great, and too like that of toluene, for inductive effects to be the only factor determining reactivity *para* to the *tert.*-butyl group.

Although this view is still, in the writer's assessment, a matter of opinion, it is certainly not contradicted, and might perhaps be held to receive some support, from later experimental developments in this field. These illustrate the way in which alkyl groups promote *para* as compared with *meta* substitution, when reagents of different charge types are used. Partial rate factors for nitration[2] by NO_2^+, for bromination[6] by Br^+ and for chlorination[8] by Cl_2 are given in Table 1, and are plotted in Fig. 1 to show the relationship:

$$\log_{10} f_m = \text{const. } \log_{10} f_p \qquad (1)$$

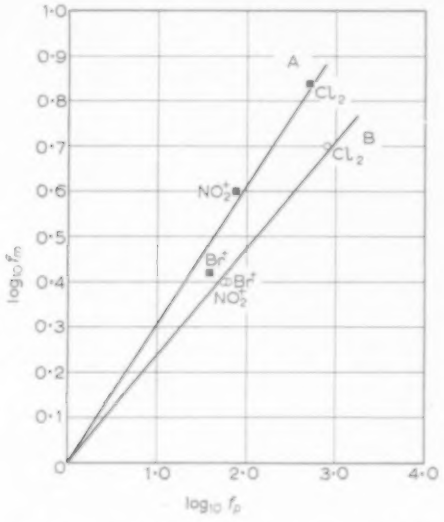


FIG. 1. Partial rate factors for substitution in: A, *tert.*-butylbenzene; B, toluene.

TABLE 1. PARTIAL RATE FACTORS FOR SUBSTITUTION IN ALKYLBENZENES

Compound	Reagent	f_m	$\log_{10} f_m$	f_p	$\log_{10} f_p$
Toluene	NO_2^+	2·5	0·40	58	1·76
	Br^+ (or $BrOH_2^+$)	2·5	0·40	59	1·77
	Cl_2	5·0	0·70	820	2·91
tert.-Butylbenzene	NO_2^+	4·0	0·60	75	1·88
	Br^+ (or $BrOH_2^+$)	2·6	0·42	38·5	1·59
	Cl_2	6·9	0·84	503	2·70

If the methyl group promoted reactivity considerably by a conjugative effect, but the *tert.*-butyl group only by an inductive effect, it might be expected, when reagents differing in charge type and electronic requirements were used (e.g., Cl_2, Br^+), that different

patterns would be obtained with the two substituents. In fact, both groups show in plots of equation (1) a reasonably good linear relationship.

A view essentially similar to that propounded by Berliner and Bondhus has recently been advocated by Brown and his co-workers[12] in regard to the relative rates of hydrolysis of the *para*-alkyl-substituted phenyldimethylcarbinyl chlorides. It is suggested that the inductive effect should be transmitted to the *para*-position no more strongly than to the nearer *meta* position, and hence that the considerable activation of the *para* position by the *tert.*-butyl group must be largely of a conjugative nature.

Structural effects on C–H *hyperconjugation*

In another paper presented at this Conference, J. W. Baker* deals in detail with the evidence that hyperconjugation from groups of the type CH_2R is affected by the nature of the group R. The direction of the change is that electron-withdrawing groups, which increase the acidity of the CH_2 hydrogen atoms, increase the hyperconjugative power of the group.[13] A qualitative indication of this can be seen, perhaps, in the fact that groups such as CH_2CO_2Et and CH_2Cl, are still mainly *o,p*-directing, though they decrease, or only slightly increase, the reactivity of the aromatic nucleus.[14]

O–H *hyperconjugation*

It has long been recognised that phenols are more reactive than their alkyl ethers in many electrophilic substitutions. But, since a number of these reactions (e.g., diazo coupling) which proceed in alkaline solution clearly involve the still much more reactive phenoxide ion, it has not so readily become recognised that the neutral phenol molecule, for example, is more reactive than anisole.

Such is, in fact, the case, however. The first kinetic investigation to establish this phenomenon was only of a preliminary nature,[4] but it established the key point, that phenol is brominated by molecular bromine in acetic acid about ninety times more rapidly than anisole, and that the rate of reaction is not depressed by the addition of sulphuric acid to the reaction medium.

Since that time, the kinetic form for the bromination of phenol has been examined by other workers in more detail;[15] within the limits imposed by the experimental technique, it resembles precisely that of anisole. The rate-comparison applies to the region of concentration in which the rate has the kinetic form: $-d[Br_2]/dt = k[ArH][Br_2]$. No indication is found of a fall-off in rate, specific to phenol, resulting from the HBr produced in the reaction. The rate-sequence, phenol > anisole, holds also for iodine-catalysed bromination in aprotic solvents.

Bromination is not the only electrophilic aromatic displacement for which the same rate-sequence has been established. Eaborn[16] has studied the proto-desilylation of a series of substituted phenyltrimethylsilanes, and has established that the reaction is promoted much more powerfully by the hydroxyl than by the methoxyl group, as is shown in the following values:

* Paper by J. W. Baker, page 135 of this volume.

[12] H. C. Brown, J. D. Brady, M. Grayson and W. H. Bonner, *J. Amer. Chem. Soc.* **79**, 1897 (1957).
[13] J. W. Baker, J. A. L. Brieux and D. G. Saunders, *J. Chem. Soc.* 404 (1956).
[14] C. K. Ingold and F. R. Shaw, *J. Chem. Soc.* 575 (1949).
[15] L. M. Yeddanapalli and N. S. Gnanapragasam, *J. Chem. Soc.* 4934 (1956).
[16] C. Eaborn, *J. Chem. Soc.* 4858 (1956); C. Eaborn and D. E. Webster, *Ibid.* 4449 (1957).

REACTION OF p-R·C_6H_4·$SiMe_3$ WITH H^+

R	p-NMe_2	p-OH	p-OMe	p-Me	p-Bu^t	H	p-Cl
Relative rate	ca. 3×10^7	10,700	1510	21·1	15·6	1	0·13

The kinetic forms for proto-desilylation are such that the acid catalysis of the reaction is the same for both the hydroxyl and methoxyl substituents, a result which confirms that the reaction of the former compound involves the activation by the OH, rather than by the O^-, substituent.

A similar result has been established for deuterium exchange,[17] though here only *ortho* substitution has been investigated. Estimates of the relative electron-releasing power of hydroxyl and methoxyl groups have also been made by Deno and his co-workers[18] from data on equi'ibria of the type $Ar_3C{\cdot}OH + H^+ \rightleftharpoons Ar_3C^+ + H_2O$. These, expressed in terms of electrophilic substituent constants, σ^+, are: OH, −0·82; OMe, −0·64. The hydroxyl group is, by this criterion also, the more powerfully electron releasing.

Expected inductive effects

It is natural to enquire how the inductive effects of hydroxyl and methoxyl groups would be expected to affect the relative reactivities in the absence of conjugative factors. The most reliable estimates of the relative inductive effects of these groups seem to be those given in McDaniel and Brown's recent compilation.[19] They are derived from the thermodynamic dissociation constants of *meta*-substituted benzoic acids, and in terms of Hammett's σ values, σ_m, are: OH, +0·121; OMe, +0·115. The methoxyl group is slightly less electron withdrawing than the hydroxyl group, just as the CH_2Me group is slightly more electron releasing than the CH_3 group. Values for σ_p (OH, −0·37; OMe, −0·27) are, as would be expected from the foregoing discussion, in the opposite direction; these indicate once again the superior conjugative power of the OH group.

It is also necessary to enquire how substituents attached to the OPh group would normally influence the rate of substitution in the phenyl group. This matter has been extensively documented, for chlorination of ethers and anilides, by Bradfield, Jones and their co-workers.[20] The changes in reactivity normally follow the inductive effect of the substituent; inductively electron-releasing groups enhance reactivity, and inductively electron-withdrawing groups diminish it, as is shown by the following sequence:

RELATIVE RATES OF CHLORINATION OF AROMATIC ETHERS, ROAr, IN ACETIC ACID

R	Pr^i	Et	Me	p-$MeC_6H_4{\cdot}CH_2$	Ph·CH_2	p-Cl·$C_6H_4{\cdot}CH_2$	p-$NO_2{\cdot}C_6H_4{\cdot}CH_2$
Relative rate	440	199	100	95	68	41	14

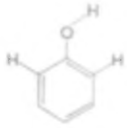
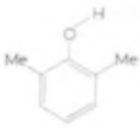
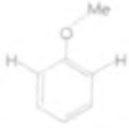
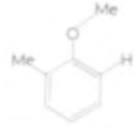
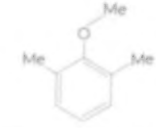
[17] D. P. N. Satchell, *J. Chem. Soc.* 3911 (1956).
[18] N. C. Deno and W. L. Evans, *J. Amer. Chem. Soc.* **79**, 5804 (1957); N. C. Deno and A. Schriesheim, *Ibid.* **77**, 3051 (1955).
[19] D. H. McDaniel and H. C. Brown, *J. Org. Chem.* **23**, 420 (1958).
[20] A. E. Bradfield and B. Jones, *Trans. Faraday Soc.* **37**, 726 (1941).

Steric inhibition of resonance

Neither an unexpected inductive sequence, nor an unexpected effect of inductive substituents on electron release from OR groups, seems to provide an explanation of the superiority in this respect of hydroxyl over methoxyl.

We have therefore given consideration to the possibility that there is sufficient steric interaction between the OMe group and the hydrogen atoms *ortho* to it to reduce substantially the ease with which the activating group may indeed make a contribution to the observed rate difference. In Table 2 are given some new experimental data for the rates of bromination, in acetic acid at low concentrations, of methyl-substituted phenols; corresponding data are also given for substituted anisoles studied by Baddeley and his co-workers.[21]

TABLE 2. RELATIVE REACTIVITIES, WITH MOLECULAR BROMINE, OF PHENOL, ANISOLE AND THEIR *ortho*-METHYL DERIVATIVES

Compound			
Relative rate of bromination	90	450	550
Compound			
Relative rate of bromination	1	6·3	0·39

All these compounds undergo bromination substantially in the 4-position,[22] so we can consider that the given relative rates refer to substitution *para* to the activating group. The introduction of a single *o*-methyl group does not prevent the approach towards coplanarity; so 2-methylanisole reacts with bromine about six times more rapidly than anisole; and *o*-cresol, about five times more rapidly than phenol. This factor of about five is very similar to that which represents the effect of a *meta*-methyl group in the bromination and chlorination of the methylbenzenes, and gives reasonable assurance that the principle that free energies of substitution are additive applies in the phenol series as in the anisole series.

A second methyl group, *ortho* to the activating group and *meta* to the position of substitution, should on this basis increase the reactivity by a further factor of five, to a relative rate (Ph · OH = 90) of about 2300. In fact, the second methyl group only

[21] G. Baddeley, G. Holt, N. A. P. Smith and F. A. Whittaker, *Nature, Lond.* **168**, 386 (1951); G. Baddeley, N. A. P. Smith and M. A. Vickars, *J. Chem. Soc.* 2455 (1956).

[22] T. Zincke and A. Hedenström, *Liebigs Ann.* **350**, 274 (1906); A. F. Holleman and I. J. Rinkes, *Rec. Trav. Chim. Pays-Bas* **30**, 48 (1916); P. B. D. de la Mare and C. A. Vernon, *J. Chem. Soc.* 1764 (1951); K. Auwers and T. Markovits, *Ber. Dtsch. Chem. Ges.* **41**, 2336 (1908); A. N. Meldrum and M. S. Shah, *J. Chem. Soc.* **123**, 1982 (1923).

slightly enhances the reactivity. So one can attribute to steric inhibition, by a H——Me repulsion, of electromeric electron release, a reduction in rate by a factor of about four.

In anisole, the steric hindrance, additional to that in phenol, to attainment of planarity results also from a single H——Me repulsion. It must, therefore, be energetically very similar in magnitude to that in 2:6-dimethylphenol. So a reduction in rate by a factor of about four might be assigned to this cause. In fact, the rate factor is about ninety. It seems very unlikely that the whole, or even a large part, of this difference arises because of deficiencies in our assumptions; and hence it is suggested that a large portion of this rate-factor of twenty-two is to be attributed to OH hyperconjugation.

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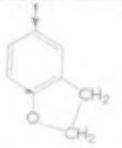
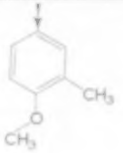
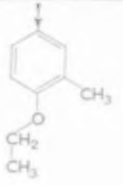
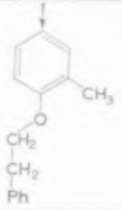
It is clear, of course, that steric inhibition of conjugation plays a part in determining these rate sequences. This is further confirmed by the small reactivity of 2:6-dimethylanisoles; the latter compound is about ninety times less reactive than would have been expected allowing for activation by two methyl groups *meta* to the position of substitution. Here the rate-reduction results from one Me——Me repulsion, and it is to be noted that even this interaction only causes about as much rate reduction as results from the replacement of the phenolic hydrogen in phenol by a methyl group.

We have deduced that a rate-reduction of about four may be attributed, in anisole, to steric inhibition of mesomerism. It is interesting to examine whether in a suitable cyclic ether the rate can be enhanced by holding the alkoxyl group in its best position for conjugation. Baddeley and his co-workers[21] have provided evidence on this point by measuring the rate of reaction of coumaran. Relative reactivities of this and of analogous compounds[20,21] are shown in Table 3.

TABLE 3. RATE OF REACTION OF COUMARAN AND ANALOGOUS COMPOUNDS

Compound				
Relative reactivity*	76	6·3	12·6†	7·5†

* Baddeley *et al.*[21]
† Estimated from data given by Bradfield *et al.*[20]

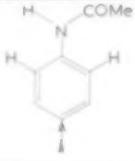
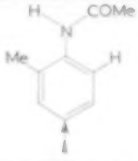
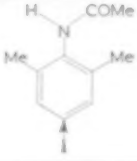
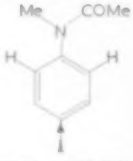
If we regard ethyl *o*-cresyl ether as the correct standard of comparison, the ring compound is more reactive by a factor of about six. If we regard 2-phenylethyl *o*-cresyl ether as a more satisfactory basis, the corresponding factor is about ten. Agreement with the small factor of four is sufficiently good to give us confidence that some reason other than steric inhibition of mesomerism must be sought for the great reactivity of phenol as compared with anisole.

The stereochemistry of the OH group in phenol needs to be considered in relation

to the possibility of OH hyperconjugation. It would seem to be generally considered that OH hyperconjugation requires that the hyperconjugating bond be out of the plane of the benzene ring. If OH hyperconjugation is important, therefore, the OH bond cannot be accurately in the plane of the ring in the transition state adopted for bromination of phenol; and a substantial contribution to the rate comes by way of activation from conformations in which the OH bond, and therefore also the axes of the lone pairs of electrons, are out of the plane of the ring. This does not seem in our view to be improbable; positions which allow the OH bond to hyperconjugate also allow the lone pairs of electrons to conjugate, though imperfectly; but the position which forces the OH bond out of hyperconjugation also can be regarded as holding one of the lone pairs of electrons in an unsuitable geometrical position. It is to be noted also that the total activation of the nucleus by the hydroxyl group is represented by a rate factor of about 10^{10};[12] the contribution attributed to the OH hyperconjugation, a factor of about twenty, is only a very small part of this.

Evidence relating to NH hyperconjugation is of a similar nature. Partial rate factors for the chlorination of acetanilide and 2-methylacetanilide are now available,[23] as shown, with that for N-methylacetanilide,[24] in Table 4.

TABLE 4. PARTIAL RATE FACTORS FOR CHLORINATION, *para* TO THE NRAc GROUP, OF ANILIDES IN ACETIC ACID AT 25°

Compound				
Partial rate factor	24×10^5	$6{\cdot}2 \times 10^5$	$0{\cdot}012 \times 10^5$	ca. $0{\cdot}02 \times 10^5$

The bulky acetyl group ensures in this series that the introduction of a single methyl substituent in the *ortho* position has a secondary steric effect by introducing hindrance to adoption of a planar configuration. One such group reduces the reactivity by a factor of about twenty, when allowance is made for the expected activation of the position of substitution, *para* to the directing group and *meta* to the methyl group, by a factor of about five. In N-methylacetanilide, on the other hand, the steric impedance to coplanarity must be of magnitude similar to that in 2-methylacetanilide, but the reactivity is very considerably diminished; by a rate-factor of about 1000. So a diminution in rate by a factor of about forty has to be given some alternative explanation, and it is suggested that this is the result of NH hyperconjugation. It is suggested also that part of the reason why this factor seems to be rather larger than for phenol is because the adoption of a coplanar conformation is energetically more difficult in the anilide series, when such a conformation requires that the H and the COMe groups are coplanar; so there is relatively greater activation by the lone pair of electrons from such non-coplanar conformations, and hence a greater opportunity for NH hyperconjugation because the stereo-electronic requirements are more suitable.

[23] P. B. D. de la Mare and M. Hassan, *J. Chem. Soc.* 1519 (1958).
[24] A. E. Bradfield and B. Jones, *J. Chem. Soc.* 3073 (1928).

The evidence relating to electron release from amino and methylamino groups seems to be less decisive. The Hammett σ_p values[19] fall at least partly in the inductive order (NH_2, −0·66; NHMe, −0·84; NMe_2, −0·83). It is of interest ,however, that Berliner and Monack[25] have found, for the reaction of 4-substituted-2-nitrobromobenzenes with piperidine, a notable reversal of the inductive order of electron release for the extremes of these groups.

To summarise, therefore, the following conclusions are drawn:

(*a*) There is good experimental evidence, both from measurements of equilibria and from reactivities, that the hydroxyl group releases electrons to a position conjugated with it more effectively than does the methoxyl group.

(*b*) There are indications that the corresponding phenomenon also occurs with the related nitrogen substituents.

(*c*) Although part of this difference is attributable to steric inhibition of resonance, estimates of the quantitative magnitude of the latter contribution suggest that some other fact also contributes strongly to the difference.

(*d*) It is not unreasonable to identify this factor with OH or NH hyperconjugation.

[25] E. Berliner and L. C. Monack, *J. Amer. Chem. Soc.* **74**, 1574 (1952).

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SECONDARY HYDROGEN ISOTOPE EFFECT IN A GAS-PHASE EQUILIBRIUM*

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THE following is a preliminary report of a study of the secondary isotope effect on a gas-phase equilibrium.

The substitution of β deuterium for hydrogen atoms in reactions in which the transition states possess considerable carbonium ion character leads to a reduction in the reaction rate.[1,2] Considerable evidence indicates that this isotope effect is associated with hyperconjugation stabilization of the carbonium ion-like transition states.†

Since the proposed relation between hyperconjugation and the secondary isotope effect has been investigated only for reaction rates in solution, an important test of the scope of the theory is provided by an investigation of the secondary isotope effect on the position of equilibrium in an appropriate gas phase reaction.

In carrying out such an investigation we have selected as a model for a hyperconjugated system the Lewis acid, $B(CH_3)_3$. An appropriate equilibrium is the Lewis acid–base reaction of the class investigated so extensively by H. C. Brown and his students:[3]

$$B(CH_3)_{3(g)} + :N(CH_3)_{3(g)} \rightleftarrows (CH_3)_3B:N(CH_3)_{3(g)} \quad (1)$$

According to hyperconjugation theory,[4] hyperconjugation stabilization of $B(CH_3)_3$ is expected to be appreciably greater than that for the addition compound, $(CH_3)_3B:N(CH_3)_3$, since the open orbital on boron in the former compound is involved in bond formation with nitrogen in the latter. Consequently, the theory of the secondary isotope effect anticipates that substitution of the β-hydrogen atoms of $B(CH_3)_3$ by deuterium (which is expected to reduce hyperconjugation preferentially in the reactant molecule of the above reaction) should shift the equilibrium (1) towards the addition compound. In other words the equilibrium constant for the following reaction (designated as K_D/K_H) should be greater than unity:

$$B(CD_3)_{3(g)} + (CH_3)_3B:N(CH_3)_{3(g)} \rightleftarrows B(CH_3)_{3(g)} + (CD_3)_3B:N(CH_3)_{3(g)} \quad (2)$$

* This work was supported in part by the office of Naval Research. Reproduction in whole or in part is permitted for any purpose of the United States Government.

† For reviews of this subject see papers of E. S. Lewis on page 143 and V. J. Shiner, Jr., elsewhere in this volume.

[1] V. J. Shiner, Jr., *J. Amer. Chem. Soc.* **75**, 2925 (1953); *Ibid.* **76**, 1603 (1954).

[2] E. S. Lewis and C. E. Boozer, *J. Amer. Chem. Soc.* **76**, 791 (1954).

[3] H. C. Brown, D. H. McDaniel and O. Häfliger, *Determination of Organic Structures by Physical Methods* (Edited by E. A. Braude and F. C. Nachod) pp. 634–643. Academic Press, New York (1955).

[4] R. A. Mulliken, C. A. Rieke and W. G. Brown, *J. Amer. Chem. Soc.* **63**, 41 (1941); J. W. Baker, *Hyperconjugation*. Oxford University Press (1952); C. A. Coulson and V. A. Crawford, *J. Chem. Soc.* 2052 (1953); Y. I'Haya, *J. Chem. Phys.* **23**, 1165, 1171 (1955); M. M. Kreevoy and H. Eyring, *J. Amer. Chem. Soc.* **79**, 5121 (1957).

Using a slightly modified procedure described by Brown *et al.*,[3,5] we have determined the equilibrium constants for reaction (1) over the temperature interval 65–95° with both $B(CH_3)_3$ and $B(CD_3)_3$, the sample of the latter compound containing no more than one per cent hydrogen. The values obtained for the former compound are in satisfactory agreement with those reported by Brown *et al.*[5] and those obtained with the latter compound give $K_D/K_H = 1{\cdot}25 \pm 0{\cdot}03$.

These results are thus in accord with the prediction of the hyperconjugation theory of the secondary isotope effect. Whatever the cause of the favorable formation of the *heavy* addition compound, $(CD_3)_3B{:}N(CH_3)_3$, the effect is actually larger than is apparent in the above value of K_D/K_H. The mass effect contribution of the translational entropy change to the equilibrium constant of reaction (2) is:

$$\left[\frac{M_{B(CH_3)_3}M_{(CD_3)_3BN(CH_3)_3}}{M_{B(CD_3)_3}M_{(CH_3)_3BN(CH_3)_3}}\right]^{3/2} = 0{\cdot}89$$

That is, the mass effect on the translational entropy favors the *light* addition compound by 11 per cent. It is probable that the mass effect on the rotational entropy change also favors the *light* addition compound, though by not as large a factor. The proposed greater inductive electron-releasing ability of deuterium than hydrogen,[6] if significant, would also favor the *light* addition compound. Thus there is an effect (or effects) favoring the *heavy* addition compound by at least 36 per cent in the equilibrium constant (or $>$ 200 cal/mole in $-\Delta F°$). We hope to be able to identify these effects upon completion of an examination of the spectra of the compounds involved in reaction (2).

[5] H. C. Brown, H. Bartholomay, Jr. and M. D. Taylor, *J. Amer. Chem. Soc.* **66**, 435 (1944).
[6] E. A. Halevi and M. Nussim, *Bull. Res. Council Israel* **A5**, 263 (1956); *Ibid.* **6**, 167 (1957); E. A. Halevi, *Tetrahedron* **1**, 174 (1957); G. V. D. Tiers, *J. Amer. Chem. Soc.* **79**, 5585 (1957).

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BOND LENGTHS AND HYPERCONJUGATION

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Among the data first cited as supporting the concept of hyperconjugation were the observations on bond lengths reported by Pauling *et al.*[1] in 1939. Nineteen years have elapsed, so it is useful to review the evidence which this criterion provides.

According to standard theory, if hyperconjugation really occurs we should expect that:

(1) When a methyl group is hyperconjugated with a triple bond, a double bond or even another methyl group, the bond joining it to this system should be shorter than normal.

It is immediately apparent that we may have difficulty in detecting an anomaly in the last case, because such a bond would naturally be taken as a standard itself; but at least we could detect anomalies relative to it.

(2) Some effect on the bonds in the rest of the system should be apparent. We should expect some degree of lengthening.

(3) If the symmetry of the methyl group is destroyed by substituting a methyl group for a hydrogen atom, to make an ethyl group, or if all three hydrogens are thus substituted to make a *tert.*-butyl group, hyperconjugation should be destroyed or at least reduced. The length of a bond joining such a group to an unsaturated system should therefore be normal, or more normal, in length.

(4) A perfluoromethyl group should also hyperconjugate; and the bond joining it to the rest of the system should therefore show shortening. Since, however, it attracts electrons, instead of repelling them as a methyl group is often supposed to do, it may produce rather different changes in the other parts of the system.

(5) The longer the hyperconjugated system is, the more will be the anomalies, particularly at its ends. Cross hyperconjugation effects should diminish it, just as happens in ordinary, or first-order, conjugation.

(6) The methyl group, or the perfluoromethyl group, might itself show anomalous lengths and bond angles as a result of hyperconjugation.

These points have been clearly realised for a long time, and many investigations have been made to test them. The more obviously relevant results are collected in Tables 1 to 6 and are discussed *seriatim*.

It is not clear what one looks for in the saturated compounds. If theoretical estimates of C–C bond order could be made for the different compounds, the lengths might be compared on this basis. The most immediate conclusion, however, is that the distances are all the same to within 0·005 Å save in CF_3–CH_3, in which it is shortened by about 0·04 Å.

[1] L. Pauling, H. D. Springall and K. J. Palmer *J. Amer. Chem. Soc.* **61**, 927 (1939).

TABLE 1. SATURATED COMPOUNDS

C–C (average) = 1·541 ± 0·003 Å[2]

C–C (diamond) = 1·54451 ± 0·00014 Å[2]

Compound*	C–C (Å)	C–H (Å)	∠HCH	C–F (Å)	∠FCF	Method of measurement
CH_3–CH_3	1·543	1·102	109·3°	—	—	Infra-red spectrum[2]
	(1·536 ±0·016)	—	—	—	—	Electron diffraction[3]
CF_3–CH_3	(1·512 ±0·014)	—	—	—	—	Electron diffraction[3]
	1·492	1·078	109° 31′	1·348	106° 42′	Microwave spectrum[4]
CHF_3	—	1·098	—	1·332 ±0·008	108·8° ±0·75°	Microwave spectrum[5]

* The values for propane and for *n*-butane are not accurate enough to provide useful comparisons.

Brockway and his co-workers have shown[5,6,7] that a CF_3 group often causes the fourth bond formed by the carbon atom to be shorter than that formed by a CH_3 group by about this amount (e.g., for C–F, C–Cl, C–Br and C–I by 0·068, 0·033, 0·029 and 0·009 Å respectively). Hence there is nothing which need be ascribed particularly to hyperconjugation, save in so far as the shortening is more than would be expected from the electronegativity of carbon.

∠ FCF is probably less in CH_3CF_3 than it is in CHF_3 or in $CClF_3$ (108·6° ±0·4). This may indicate something: but it is not an obvious electrostatic result of more negative charge on the fluorine atoms.

Duchesne has suggested[8] that this reduction of angle causes an increase of *s* character in the fourth (the C–C) bond, which may account for the shortening. This, however, leaves unexplained the reduction of angle: in an earlier communication[9] he concluded that increase of electronegativity of the halogen in the methyl halides causes a decrease in the degree of *p* character in the C-halogen bond. An increase of *p* character would seem to be required to explain the angle reduction by a change of hybridisation.

This observation might be attributed to hyperconjugation.

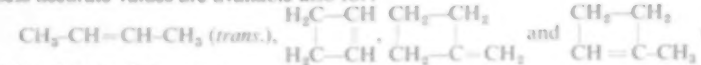
In the olefines, recent measurements have shown that the C–C = bond is distinctly shorter than the paraffinic bond, by about 0·05 Å. There appears to be a lesser contraction in the C–C_6H_5 bond, of about 0·02 Å; but there is a dearth of good measurements for it.

[2] *Interatomic Distances in Molecules and Ions. Special Publication* No. 11, The Chemical Society, London (1958).
[3] L. O. Brockway and R. H. Schwendeman, personal communication.
[4] L. F. Thomas, J. S. Heeks and J. Sheridan, *Z. Electrochem.* **61**, 935 (1957).
[5] L. O. Brockway and R. Anderson, personal communication.
[6] L. O. Brockway and C. Thornton, personal communication.
[7] L. S. Bartell and L. O. Brockway, *J. Chem. Phys.* **23**, 1860 (1955).
[8] J. Duchesne, *J. Chem. Phys.* **20**, 540 (1952).
[9] J. Duchesne, *Nature, Lond.* **159**, 62 (1947).

Table 2. Olefines*

Compound†	C–C (Å)	C=C (Å)	C–H methyl (Å)	∠HCH methyl	Method of measurement
$CH_2=CH_2$	—	(1·334)	[(1·085)]‡	[(116°)]‡	Electron diffraction[10]
	—	(1·337)	[(1·086)]‡	[(117° 22′)]‡	Infra-red spectrum[11]
$CH_3–CH=CH_2$	1·488	1·353	1·090 (ass.)	107° 11′	Microwave spectrum[12]
	(1·49)	—	—	—	Electron diffraction[13]
$(CH_3)_2CH=CH_2$	(1·50)	—	—	—	Electron diffraction[13]
$CH_3–CH=CH–CH_3$ (*cis*)	(1·51)	—	—	—	Electron diffraction[13]
$CH_3–CH=C=CH_2$	1·48§	—	—	—	Microwave spectrum[14]

* Aromatic: C–C in C–Ph = 1·52$_5$ ± 0·01 (average).
† Less accurate values are available also for:



(Ref. 2).
‡ Values for the CH_2 groups.
§ Consistent with the observations.

These anomalies could be due to hyperconjugation; but there are two other causes which must be considered. One is that the covalent radius of carbon is reduced when the hybridisation changes[15] from sp^3 to sp^2, and the other is that the difference of electronegativity, arising from the same cause, results in a contraction of bond length.[11] A difference of about 0·5 of Pauling's electronegativity units would be required to explain the whole of this contraction; this seems high.

Concerning the effect of hybridisation, it may be noted that very recent measurements on butadiene ($CH_2=CH–CH=CH_2$) by O. Bastiansen (personal communication) give a value of 1·483 ± 0·003 Å for the central bond; so if the *whole* of the contraction of 0·06 Å in this bond relative to the paraffinic standard be attributed to change of carbon radii, the change is −0·03 Å in each, leaving only −0·02 Å to be explained by electronegativity difference in the methyl–ethylene bond. From the C–H bond lengths in methane and in ethylene (r_0 = 1·091 and 1·07 Å respectively) the change of carbon radius appears to be −0·02 Å: so there is fair agreement between the two estimates.

∠ HCH in methyl seems to be smaller (107° 11′) than the tetrahedral value if the C–H bond length is assumed to be 1·090 Å.

It is not certain if the C=C bond length is increased relative to ethylene, for the

[10] L. S. Bartell and R. A. Bonham, *J. Chem. Phys.* **27**, 1414 (1957).
[11] H. C. Allen and E. K. Plyler, *J. Amer. Chem. Soc.* **80**, 2673 (1958).
[12] D. R. Lide, Jr. and D. E. Mann, *J. Chem. Phys.* **27**, 868 (1957).
[13] See E. Goldish, K. Hedberg and V. Schomaker, *J. Amer. Chem. Soc.* **78**, 2714 (1956).
[14] D. R. Lide, Jr. and D. E. Mann, *J. Chem. Phys.* **27**, 874 (1957).
[15] C. A. Coulson, *Victor Henri Mem. Vol.* p. 15. Desoer, Liège (1948).

error in the propylene measurement is not given. The value tried therein was the older one[2] of 1·353 Å: a much shorter one appears not to have been tried.

In the related compound, acetaldehyde, the C–C bond is somewhat less shortened, by 0·04 instead of 0·05 Å. The opposite would be expected if difference of electronegativity were the cause, for this should be increased by the attachment of =O instead of $=CH_2$ to the middle carbon atom. Possibly, therefore, shortening by electronegativity difference is not important.

TABLE 3. ALDEHYDES

Compound	C–C (Å)	C=O (Å	∠CCO	CH (Å)	∠HCH	CH (Å)	∠CCH	Method of measurement
CH_3–CH=O	1·500$_5$ ±0·005 (1·504)	1·215$_5$ ±0·002 (1·208)	123° 55′ ±6′ (123° 36′ ±90′)	1·086 ±0·005	108° 16′ ±15′	1·114 ±0·015	117° 29′ ±45′	Microwave spectrum[16] Electron diffraction[16]
C–C=O (various)	1·516 ±0·005 (average)							Reference 2
CF_3–CH=O	(1·54 ±0·02)							Electron diffraction[3]

The bond length in trifluoroacetaldehyde is equal to the paraffinic standard, i.e., the fourth bond formed by the perfluoromethyl carbon atom is now longer than that formed under the same conditions by the methyl carbon atom. This, as Brockway has pointed out (personal communication), is the opposite of what is normally found (see above); so it can hardly be explained by a normal change of atomic radius due to fluorine substitution. It could indicate an absence of hyperconjugation caused by the unwillingness of the CF_3 group to part with electrons as required by the –CH=O group, i.e., to mutual incompatibility.

The C–H bond length in the methyl group (1·086 Å) is very slightly shorter than that in methane (r_0 = 1·091 Å), and ∠HCH (108° 16′) is slightly less than tetrahedral.

There are therefore some anomalies which do not agree with ideas of fixed radii or with shortening by electronegativity difference. Another point to note is that ∠CCC in propylene is 124° 45′ and ∠CCO is 123° 16′ in acetaldehyde compared with 121° 19′ for ∠CCH in ethylene: these might indicate a tendency to an allene-like structure.

In the several acetylenes which have been measured, the striking feature is the essential constancy of the C–C bond length, at 1·456 ± 0·002 Å. This is 0·087 Å shorter than the paraffinic standard.

Unfortunately, errors are not usually ascribed in microwave measurements; so the real significance of this observation is not quite clear. Fluorine substitution in methyl may possibly cause a small increase, but substitution by bromine or chlorine of the acetylenic hydrogen causes no change, although there is evidence from electric dipole moment measurements that a considerable degree of conjugation or other disturbance results. It is a striking fact that the mean of the C–C paraffinic standard (1·543) and of the C–C bond between two triple bonds

[16] R. W. Kilb, Chun Chia Lin and E. B. Wilson, Jr., *J. Chem. Phys.* **26**, 1695 (1957).

TABLE 4. ACETYLENES

Compound	C–C (Å)	C≡C (Å)	C–H methyl (Å)	∠HCH	C–H –yne (Å)	Method of measurement
H–C≡C–H	—	1·201	—	—	1·064	Infra-red spectrum[2]
CH_3–C≡C–H	1·458	1·207	1·112 (D)1·108	108·4°	1·060	Microwave spectrum[2]
CH_3–C≡C–CH_3	1·457	1·211	—	—	—	X-ray crystallography[17]
CF_3–C≡C–H	1·464 ±0·02	1·201 ±0·002	(F)1·33$_5$ ±0·01	(F)107·5° ±1°	1·056 ±0·005	Electron diffraction + microwave spectrum[2]
CF_3–C≡C–CH_3	1·455	1·189	1·097 (F)1·340	108° 30′ (F)106° 8′	—	Microwave spectrum[18]
CH_3–C≡C–Br	(1·458)	—	—	—	—	Microwave spectrum[19]
CH_3–C≡C–Cl	1·458	—	1·117	108° 8′	—	Microwave spectrum[20]
(H–C≡C–)$_2$	—	1·205 (ass.)	C–C = 1·379		1·064 (ass.)	Infra-red spectrum[2]
1·456 1·375 1·059 CH_3–C≡C–C≡C–H 1·208 1·209			1·111 (D)1·103	108·6°	1·059	Microwave spectrum[19]
(CH_3–C≡C–)$_2$	1·450	1·205	C–C = 1·377			Electron diffraction[21]
	1·466	1·199		1·375		X-ray crystallography[17]
(CH_3–C≡C–C≡)$_2$	1·47 ±0·02	1·20		1·38		X-ray crystallography[2]

(D) = Deuterium substituted. (F) = Fluorine substituted.

[17] E. Pignataro and B. Post, *Acta Cryst.* **8**, 672 (1955).
[18] B. Bak, D. Christensen, L. Hansen-Nygaard and E. Tannenbaum, *J. Chem. Phys.* **26**, 241 (1957).
[19] J. Sheridan, personal communication.
[20] C. C. Costain, *J. Chem. Phys.* **23**, 2037 (1955).
[21] A. Almenningen, O. Bastiansen and J. Munthe-Kaas, *Acta Chem. Scand.* **10**, 261 (1956).

(1·377) is 1·460 Å. If the 1·377 Å is a distance which includes the effect of conjugation, or increase of bond order, the 1·460 Å also includes some such increase: this is tantamount to saying that the effects of increase of bond order due to conjugation or to hyperconjugation are additive; but that might be the case. Were this so, resonance could not be demonstrated by departure from additivity; and a decision as to whether or not there is an increase of bond order would have to depend upon theoretical calculations, e.g., of overlap, or on some other experimental means of diagnosis. Alternatively, the results could be explained by fixed radii resulting from *sp* hybridisation. However, from the difference between the C–H lengths in methane and in acetylene (1·091 and 1·064 Å) the decrease in radius due to *sp* bonding would appear to be only 0·027 Å; so the apparent decrease of 0·087 Å shown in the C–C bond is not obviously due to this alone.

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If the whole contraction were a Schomaker–Stevenson contraction,[22] the electronegativity difference would have to be 1 Pauling unit.

The C–H methyl bond lengths (1·109 Å average) are about 0·02 Å longer than in methane, but a similar effect is also produced by electronegative substitution, e.g., by halogens (CH_3X, has C–H = 1·11, 1·11, 1·109 and 1·11 for Br, Cl, F and I), but ∠HCH (108·5°) is somewhat smaller than tetrahedral. The C–F bond lengths are much the same as in CHF_3, but ∠FCF (106·5°) is distinctly less than tetrahedral, and is more anomalous than it is in CHF_3 (108·8°).

Duchesne has suggested[8] that the shortening of the C–C bond can be correlated with the decreases in ∠HCH in methyl and of ∠FCF in perfluoromethyl: but this still leaves the need of an explanation for these reductions in angle (cf. p. 119).

The C≡C bond length in the substituted acetylenes shows no perceptible lengthening (average 1·203 Å) relative to that in acetylene itself.

For the cyanides there is a particularly interesting series of measurements. For methyl cyanide and for methylcyanoacetylene the C–C length is 1·456 Å, i.e., exactly the same as for the acetylenes. This suggests, again, that electronegativity difference is not the cause of the contraction. The C–H length in hydrogen cyanide (1·068 ± 0·003 Å) is essentially the same as that in acetylene 1·064 Å, also indicating that the carbon radius is unchanged by substitution of ≡N for ≡CH. As was remarked for the acetylenes, the radius change shown by this bond length is far too small to explain the observed C–C contraction. Fluorine substitution in the methyl group again may, possibly, cause an increase of length, but values are not concordant.

When the trigonal symmetry of the methyl group is broken, as in ethyl cyanide the bond length appears to increase by about 0·017 Å. According to standard theory therefore, this is all that is attributable to hyperconjugation. The remaining 0·070 Å may be due to other causes. Two preliminary results for *tert.*-butyl cyanide indicate no increase at all.

In all these compounds, the C–H bond length in the methyl group (1·104 Å) is longer than the paraffinic standard, and much the same as that in the acetylenes (1·109 Å). ∠HCH is tetrahedral. The C–F length is the same as in CHF_3, but ∠FCF is only 107·5°.

There is no perceptible lengthening of the C≡N bond in the cyanides, compared with that in hydrogen cyanide itself.

The silicon compounds shown in Table 6 indicate a contraction of the C–Si bond

[22] V. Schomaker and D. P. Stevenson, *J. Amer. Chem. Soc.* **63**, 37 (1941).

TABLE 5. CYANIDES

Compound	C–C (Å)	C≡N (Å)	C–H methyl (Å)	∠HCH	Method of measurement
H–C≡N	—	1·156 ±0·001	—	—	Microwave spectrum[2]
CH_3–C≡N	1·458	1·157	1·112 (D)1·107	109·27°	Microwave spectrum[3]
	(1·46 ± 0·01)	—	—	—	Electron diffraction[5]
CF_3–C≡N	1·46	1·153	(F)1·335	(F)107·5°	Microwave spectrum[4]
	(1·495 ± 0·014)	—	—	—	Electron diffraction[5]
CH_3–CH_2–C≡N	1·4735 1·5479 both ±0·0015	1·1566 ±0·0015	1·0914 ±0·0015	109° 19′ ±10′	∠CCC= 110° 32′ ±2′ Microwave spectrum[23]
$(CH_3)_3$C–C≡N	(1·460) (Bu) (1·540)	(1·158)	(1·110)	(109·5°)	(109·5°) Microwave spectrum[24]
	(1·46 ± 0·02) (Bu) (1·54 ± 0·01)	(1·16 ± 0·07)	—	(∠CCC)	(109·5°) Electron diffraction[25]
1·208 CH_3–C≡C–C≡N 1·374	1·454	1·159	—	—	Microwave spectrum[19]

(D) = Deuterium substituted. (F) = Fluorine substituted. (Bu) = C–C in the *tert*-butyl group.

[23] R. G. Lerner and B. P. Dailey, *J. Chem. Phys.* **26**, 678 (1957).
[24] J. Sparstad and E. Amble, *J. Chem. Phys.* **27**, 317 (1957).
[25] R. L. Livingston and C. N. R. Rao, personal communication.

TABLE 6. SILICON COMPOUNDS

Compound	C–Si (Å)	Si–H (Å)	∠HSiH	C–H (Å)	∠HCH	Method of measurement
CH_3–SiH_3	1·8668 ±0·0005	1·485 ±0·005	108° 15′ ±30′	1·093 ±0·005	107° 40′ ±30′	Microwave spectrum[28]
C_6H_5–SiH_3	1·84 ±0·01	—	—	—	—	Electron diffraction[3]

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by about 0·027 Å in the aromatic compound, which is about the same as that at present reported in methylated aromatics. This could be due to a change in carbon covalent radius.

Considering these results as a whole, it is difficult to avoid concluding that no consistent explanation can be given on the current hypotheses that atoms have constant covalent radii subject only to corrections for changes of hybridisation, differences of electronegativity and changes of bond order. It is generally appreciated that the hydrogen covalent radius is variable: thus *l*(C–H) in methane is 0·051 Å shorter than the mean of *l*(C–C) and *l*(H–H). Therefore, caution is necessary in predicting lengths of C–C bonds from observed changes in C–H bond lengths. Nevertheless, such a procedure is only to be discarded completely for our present purpose if there is reason to think that, from the C–H changes, too small contractions are predicted for the C–C bonds in olefines, acetylenes and related compounds. In fact, contractions of H–X bonds seem to be at least as large as those of C–X bonds, e.g., when X is a halogen, the anomalies relative to the mean of *l*(H–H) and *l*(X–X) are −0·162, −0·090, −0·099 and −0·096 Å for fluoride, chloride, bromide and iodide, while those relative to the mean of *l*(C–C) and *l*(X–X) in the methyl halides are,[2] respectively, −0·095, +0·021, +0·026 and +0·035 Å. Thus if the observed contraction in a C–C bond is considerably greater than that so predicted, it probably signifies something more than a general change of carbon radius due to change of hybridisation.

Electronegativity differences do not provide any consistent explanation of the remaining differences, as was seen for the aldehydes and the cyanides.

It is not satisfactory to ascribe the residual anomalies to changes of bond order arising from hyperconjugation unless they can be shown to conform to all the predictions made on this hypothesis. In the case of ethyl cyanide and *tert.*-butyl cyanide, one such is not satisfied. The increases of angle in propylene and in aldehyde do, however, satisfy qualitatively another prediction. The increases in C–H bond length in the CH_3 groups, and the changes of angle in these and in the CF_3 groups could be but do not have to be ascribed to hyperconjugation.

The general conclusion from this qualitative discussion is that hyperconjugation is not clearly and unambiguously proved by bond length anomalies to exist in the ground states of molecules, although on the other hand its existence is not certainly disproved. A more quantitative discussion would require comparisons of fact with predictions of bond length made essentially from independent data, e.g., from thermal data. Other explanations may prove possible: it can be safely said that there are indications

[28] R. W. Kilb and L. Pierce, *J. Chem. Phys.* **27**, 108 (1957).

that the effective radius of an atom in a bond depends upon the nature of the other atom in ways which have not yet been defined.*

Acknowledgement—The author is very grateful to Professor O. Bastiansen, Professor L. O. Brockway, Professor R. L. Livingston and Dr. J. Sheridan for supplying unpublished results, and to them, to Professor C. A. Coulson, F.R.S., and Dr. J. Duchesne for very helpful discussions and correspondence.

* See Duchesne[27] for another suggestion for a cause of variation in bond length.

[27] J. Duchesne, *J. Chem. Phys.* **19**, 246 (1957).

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THE THERMOCHEMICAL EVIDENCE FOR HYPERCONJUGATION

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Abstract—Thermochemical evidence pertinent to the question of hyperconjugation is reviewed with the following conclusions. The data indicate that alkyl substitution at an unsaturated linkage results in stabilization of appreciable magnitude which is essentially independent of the nature of the alkyl group and which cannot, in the general case, be accounted for in terms of steric effects. Beyond these facts the calorimetric results do not provide significant information on the nature of the stabilization process and hence cannot distinguish among various interpretations that have been advanced in explanation of this phenomenon.

IN a series of investigations commencing in 1935, Kistiakowsky and his associates obtained by direct measurement the heats of hydrogenation of several substituted olefins in the vapor phase at 82°.* An experimental precision of the order of 0·1 per cent was achieved in this work, the results of which are recorded in Table 1. Although slightly less precise values for heats of hydrogenation are obtainable by difference from the heats of formation of various olefins and those of the corresponding paraffins,[1] the quantities derived in this way in general serve only to confirm and extend the original observations of Kistiakowsky without adding anything fundamentally new to his results.

Inspection of the data of Table 1 reveals three points of major interest. First, it will be noted that the heats of hydrogenation decrease in successively smaller increments with increasing substitution of the double bond, the difference in the values for ethylene and for tetramethylethylene being 6·2 kcal/mole. A similar trend is observed in the series benzene (−49·8 kcal/mole), ethylbenzene (−48·9 kcal/mole) and mesitylene (−47·6 kcal/mole),[2] and in the heats calculated for the reactions acetylene → ethylene (−42·2 kcal/mole), propyne → propylene (−39·6 kcal/mole) and 2-butyne → *trans*-butene (−38·0 kcal/mole).[3] Secondly, the heats of hydrogenation of propylene, 1-butene, *iso*propylethylene and *tert.*-butylethylene are found to be virtually identical. It follows that, whatever the origins of the substitution effect, the net result is essentially independent of the nature of the alkyl substituent, although the *neo*pentyl group may consitute an exception deserving special consideration.

The Kistiakowsky work finally emphasizes the fact that steric interactions, which

* For a summary of a large portion of this work, see J. B. Conant and G. B. Kistiakowsky *Chem. Rev.* **20**, 187 (1937).

[1] *Selected Values of Properties of Hydrocarbons*. Circular C461 of the National Bureau of Standards, U.S. Printing Office, Washington, D.C. (1952).

[2] G. B. Kistiakowsky, J. R. Ruhoff, H. A. Smith and W. E. Vaughan, *J. Amer. Chem. Soc.* **58**, 146 (1936), and Reference 7. *o*-Xylene shows a slightly lower heat of hydrogenation (−47·3 kcal/mole) than does mesitylene. The origin of this discrepancy has not been established, although conformational factors in the reduction products may be involved.

[3] J. B. Conn, G. B. Kistiakowsky and H. A. Smith, *J. Amer. Chem. Soc.* **61**, 1868 (1939).

TABLE 1. VAPOR-PHASE HEATS OF HYDROGENATION (82°)

Compound	$\triangle H$ (kcal/mole)	Reference
Ethylene	−32·8	4
Propylene	−30·1	5
1-Butene	−30·3	5
1-Heptene	−30·1	6
*neo*Pentylethylene	−29·5	7
*iso*Propylethylene	−30·3	7
tert.-Butylethylene	−30·3	7
cis-Butene	−28·6	5
trans-Butene	−27·6	5
*iso*Butene	−28·4	5
2-Methyl-1-butene	−28·5	6
2,3-Dimethyl-1-butene	−28·0	6
2,4,4-Trimethyl-1-pentene	−27·2	7
Trimethylethylene	−26·9	6
2,4,4-Trimethyl-2-pentene	−28·4	7
Tetramethylethylene	−26·6	6

are undoubtedly the major source of the 1 kcal difference between the heats of hydrogenation of *cis*- and of *trans*-butene, cannot be disregarded, and that such factors may seriously compromise the investigation of other phenomena by the hydrogenation method. Since steric strain in the reactant will result in an increased heat of hydrogenation, whereas steric interactions in the product lower the enthalpy change for the hydrogenation process, a reduced heat of hydrogenation can be interpreted alternately on the basis of reactant stabilization or of product destabilization. A well-known example of the latter effect is the *cyclo*pentene–*cyclo*pentane case, in which eclipsing of hydrogens in the saturated product serves to depress the heat of hydrogenation of the five-ring olefin below the *cyclo*hexene value, despite the presence of greater strain in the *cyclo*pentene than in the *cyclo*hexene double bond.[3]

The effects of methyl substitution in the series ethylene, propylene, *trans*-butene, trimethylethylene and tetramethylethylene have in the past been uniformly interpreted in terms of olefin stabilization, questions of steric influence, particularly in the cases of the last two members of the group, having been neglected. Since trimethylethylene and tetramethylethylene possess, in order, one and two *cis*-butene interactions not found in the other compounds under consideration, the heats of hydrogenation

[4] G. B. Kistiakowsky, H. Romeyn, J. R. Ruhoff, H. A. Smith and W. E. Vaughan, *J. Amer. Chem. Soc.* **57**, 65 (1935).
[5] G. B. Kistiakowsky, J. R. Ruhoff, H. A. Smith and W. E. Vaughan, *J. Amer. Chem. Soc.* **57**, 876 (1935).
[6] G. B. Kistiakowsky, J. R. Ruhoff, H. A. Smith and W. E. Vaughan, *J. Amer. Chem. Soc.* **58**, 137 (1936).
[7] M. A. Dolliver, T. L. Gresham, G. B. Kistiakowsky and W. E. Vaughan, *J. Amer. Chem. Soc.* **59**, 831 (1937).

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of these substances, corrected for olefin strain, should be lower than the values actually observed by at least 1·0 and 2·0 kcal/mole, respectively. Although it seems reasonable to suppose that repulsive interactions in paraffins will also increase with branching, the fact that within a group of isomers the more highly branched members possess the greater stability (cf. Table 2) makes the estimation of steric strains in saturated systems a matter of considerable difficulty. Some efforts in this direction have nevertheless been made, notably by Spitzer and Pitzer.[6] As applied to the case of 2,3-dimethylbutane the Pitzer method is as follows. It is observed that 2-methylpentane possessing one *iso* branch is 1·7 kcal/mole more stable than *n*-hexane, the corresponding straight-chain isomer. Assuming that the effects of branching are normally additive,* 2,3-dimethylbutane with two *iso* groupings should differ from *n*-hexane by −3·4 kcal/mole and from 2-methylpentane by −1·7 kcal/mole. The latter difference is in fact only −0·8 kcal/mole, and the discrepancy of 0·9 kcal/mole is assigned in this treatment to the steric energy difference between 2-methylpentane and 2,3-dimethylbutane. The method does not, of course, given any information on the strain energies of the *iso* compounds which are employed as reference substances. A possible approach to this problem may be given along the following lines.

TABLE 2. HEATS OF FORMATION OF VARIOUS PARAFFINS[1] (VAPOR PHASE, 25°)

Compound	$\triangle H_f$	Difference from normal paraffin
n-Butane	−30·2	0
*iso*Butane	−32·2	−2·0
n-Pentane	−35·0	0
*iso*Pentane	−36·9	−1·9
*neo*Pentane	−39·7	−4·7
n-Hexane	−40·0	0
2-Methylpentane	−41·7	−1·7
2,3-Dimethylbutane	−42·5	−2·5
2,2-Dimethylbutane	−44·4	−4·4

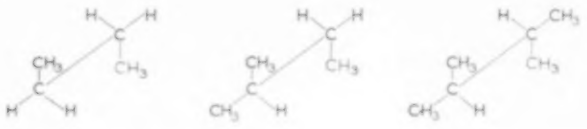
Structures (I), (II) and (III) are taken as the most stable arrangements of *n*-butane, 2-methylbutane and 2,3-dimethylbutane, respectively. Assuming that strain energy in (I) is negligible and disregarding "B-strain" in (II) and (III),[8] the differences in steric energy between (I) and (II) and between (II) and (III) may each be equated to the strain in a single skew *n*-butane structure. Since Pitzer[9] has assigned a value of 0·8 kcal

* A test of this assumption is provided by a comparison of the heats of formation of 2,5-dimethylhexane (−53·2 kcal/mole), in which the *iso* structures are widely separated, with those of 2-methylheptane (−51·5 kcal/mole) and of *n*-octane (−49·8 kcal/mole), the differences being, respectively, −1·7 and −3·4 kcal/mole (ref. 8).

[8] R. Spitzer and K. S. Pitzer, *J. Amer. Chem. Soc.* **70**, 1261 (1948); see also H. C. Brown and W. H. Bonner, *Ibid.* **75**, 14 (1953), and ref. 12.

[9] K. S. Pitzer *Chem. Rev.* **27**, 39 (1940); C. W. Beckett, K. S. Pitzer and R. Spitzer *J. Amer. Chem. Soc.* **69**, 2488 (1947).

for the energy difference between the skew and staggered arrangements of *n*-butane, the above argument suggests that repulsive energy increases in increments of approximately 0·8 kcal/mole in the sequence (I) to (II) to (III). On this basis the heats of hydrogenation of trimethylethylene and of tetramethylethylene, corrected both for olefine



(I) (II) (III)

and for paraffin strain, are −26·7 and −26·2 kcal/mole, respectively. It would therefore appear that the decrease in heat of hydrogenation that accompanies methyl substitution in this series is not of steric origin. That the effect resides specifically in an intrinsic stabilization of the olefines is most clearly demonstrated in cases where isomeric olefins differing in degree of substitution, and hence also in the nature of the alkyl substituents, yield the same reduction product. Thus the heat of hydrogenation of 1-butene (−30·3 kcal/mole) exceeds that of *trans*-butene (−27·6 kcal/mole) by 2·7 kcal/mole, a value that represents the heat of isomerization of the mono- into the di-substituted derivative. Similarly, the heats of isomerization of 2-methyl-1-butene (disubstituted) into trimethylethylene (trisubstituted) and of 2,3-dimethyl-1-butene (disubstituted) into tetramethylethylene (tetrasubstituted) are −1·6 and −1·1 kcal/mole, respectively, while the heat of isomerization of *iso*propylethylene into trimethylethylene is −3·4 kcal/mole. The pair 2,4,4-trimethyl-1-pentene and 2,4,4-trimethyl-2-pentene constitutes a special exception, which is considered in a later section of this paper.

In 1939 Mulliken suggested that the stabilizing influence of methyl substituents on ethylenic and acetylenic linkages could be explained by hyperconjugation involving α C–H bonds.[10] If the entire effect is thus assigned, hyperconjugation would involve energies of the same order of magnitude as those associated with the conjugation of two double bonds.

Numerous objections to the original Mulliken proposal have been raised in recent years. Baker[11] has noted that if branching in paraffin hydrocarbons can result in stabilization amounting to some few kcal/mole, the same factors may be responsible for stabilization of compounds possessing branches at olefinic carbon atoms.*[10] Furthermore, the fact that methyl, ethyl, *iso*propyl and *tert.*-butyl groups appear to produce equivalent effects requires an explanation beyond that provided by the C–H hyperconjugation theory. Dewar and Pettit[12] have attempted to explain stabilization both in branched paraffins and in alkyl substituted olefins in terms of second-order perturbations in adjacent bonds (H–C–H, C–C–H, C–C–C, C=C–H, C–C=C). It is noted, however, that if C–H and C–C hyperconjugation play roles of comparable importance, the adjacent bond interaction theory for olefins would be unnecessary.

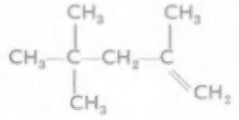
* It may be noted in this connection that *iso*butene is more stable than *trans*-butene by 1·2 kcal/mole (from free energies of formation given in reference 1).

[10] R. S. Mulliken, *J. Chem. Phys.* 7, 339 (1939); R. S. Mulliken, C. A. Rieke and W. G. Brown, *J. Amer. Chem. Soc.* 63, 41 (1941).
[11] J. W. Baker, *Hyperconjugation* p. 40. Oxford University Press (1952).
[12] M. J. S. Dewar and R. Pettit, *J. Chem. Soc.* 1625 (1954).

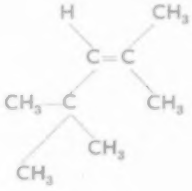
More recently, Dewar[13] has suggested that the effects conventionally ascribed to hyperconjugation in alkyl-substituted olefins, and to electronic delocalization (resonance) in systems of the butadiene type, can be interpreted on the basis of energy variations resulting from changes in hybridization. The greater stability of propylene as compared to ethylene is thus attributed to the fact that on hydrogenation the propylene C–C single bond, formed by sp^3–sp^2 overlap, is converted into an sp^3–sp^3 bond whereas in ethylene the analogous change is s–sp^2 to s–sp^3. This suggestion possesses considerable merit, although certain of Dewar's deductions regarding conjugated systems will require careful scrutiny.*

Taft and Kreevoy[14] have analyzed the Kistiakowsky data with the aid of an empirical relationship of the general Hammett form and have concluded that in cases where steric factors are unimportant the heats of hydrogenation can be correlated with a reaction parameter (ρ^*), an inductive substituent constant (σ^*), and a hyperconjugation factor (h) amounting to about 0·5 kcal for each α C–H bond. An additional parameter for C–C hyperconjugation has been employed by Taft and Lewis[15] in a discussion of hyperconjugative and inductive effects in various reactions of *m*- and *p*-alkylphenyl derivatives, but C–C hyperconjugation has not been specifically considered in the Taft treatment of the Kistiakowsky data.

In connection with a study of elimination accompanying the solvolysis of 2-halo-2,4,4-trimethylpentenes it has been noted that 2,4,4-trimethyl-1-pentene (IV) predominates over 2,4,4-trimethyl-2-pentene (V) in the olefinic portion of the reaction product.[16] Equilibration experiments[17] carried out on (IV) and (V) in 80 per cent aqueous ethanol at 25° furnish an equilibrium constant of the order of 5·7, favoring



(IV)



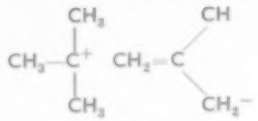
(V)

the Δ^1-product (IV). The free-energy difference between (IV) and (V) is therefore approximately 1 kcal/mole, a result that is consistent with the gas-phase data of Table 1 and with measurements of the heats of hydrogenation of (IV) and (V) carried out in acetic acid solution at 25° (Table 3).[18] The fact that in this case the disubstituted olefin is more stable than the trisubstituted isomer constitutes an important exception to the general rule. Conversion of the *tert.*-butyl groups of (IV) and (V) into *iso*propyl groups gives 2,4-dimethyl-1-pentene and 2,4-dimethyl-2-pentene in

* The fact that butadiene, which can adopt a planar arrangement, and *cyclo*octatetraene, which cannot, show closely comparable experimental stabilization energies cf. [ref.2 and R. B. Turner, W. R. Meador, W. von E. Doering, J. R. Mayer and D. W. Wiley, *J. Amer. Chem. Soc.* **79**, 4127 (1957)] appears to constitute a discrepancy in the Dewar argument, since butadiene possesses only one sp^2–sp^2 bond, whereas four such bonds are present in *cyclo*octatetraene.

[13] M. J. S. Dewar and A. N. Schmeising, *Tetrahedron* **5**, 166 (1958).
[14] R. W. Taft and M. M. Kreevoy, *J. Amer. Chem. Soc.* **79**, 4011 (1957).
[15] R. W. Taft and I. C. Lewis, *J. Amer. Chem. Soc.* **80**, in press (1958).
[16] Cf. H. C. Brown and H. L. Berneis, *J. Amer. Chem. Soc.* **75**, 10 (1953).
[17] E. D. Hughes, C. K. Ingold and V. J. Shiner, *J. Chem. Soc.* 3827 (1953).
[18] R. B. Turner, D. E. Nettleton and M. Perelman, *J. Amer. Chem. Soc.* **80**, 1430 (1958).

which the normal stability relationship is restored. In attempting to account for the anomalous behavior of (IV) and (V), Hughes *et al.*[17] noted that, although only five hydrogen atoms are available for hyperconjugation in (IV) as compared to six in (V), important contributions from form (VI) might serve to stabilize the Δ^1-olefin.



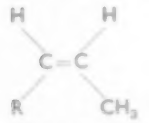
(VI)

Brown and his associates,[16,19] however, have emphasized the fact that the stability of (V) is adversely affected by the presence of a *cis*-methyl–*tert*.-butyl interaction, and that predominance of steric over hyperconjugative effects in this olefin provides a reasonable basis for interpretation of the observed stability order. Calorimetric evidence[18] on the magnitudes of interactions of this type supports the latter view.

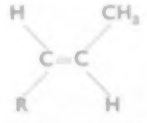
TABLE 3. HEATS OF HYDROGENATION IN ACETIC ACID SOLUTION (25°)*

Compound	$\triangle H$ (kcal/mole)	$\triangle(\triangle H)$
2,4-Dimethyl-1-pentene	−26·7	
2,4-Dimethyl-2-pentene	−25·2	−1·5
2,4,4-Trimethyl-1-pentene (IV)	−25·5	
2,4,4-Trimethyl-2-pentene (V)	−26·8	1·3
4-Methyl-*cis*-2-pentene (VIIa)	−27·3	
4-Methyl-*trans*-2-pentene (VIIIa)	−26·4	−0·9
4,4-Dimethyl-*cis*-2-pentene (VIIb)	−30·8	
4,4-Dimethyl-*trans*-2-pentene (VIIIb)	−26·5	−4·3

* Precision of the data is approximately ±0·5 per cent.



(VIIa. R = Pr^i)
(VIIb. R = Bu^t



(VIIIa. R = Pr^i)
(VIIIb. R = Bu^t)

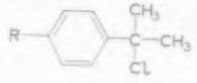
Whereas the difference between the heats of hydrogenation of the *cis*- and *trans*-4-methyl-2-pentenes (VIIa and VIIIa), in which hyperconjugative and inductive factors, hybridization effects and the like should cancel, is essentially the same as that for the *cis*- and *trans*-butenes (−1·0 kcal/mole), a considerably larger difference (−4·3 kcal/mole) is observed for the *cis*- and *trans*-4,4-dimethyl-2-pentenes (VIIb and VIIIb).*

* The fact that the heats of hydrogenation of (VIIIa) (−26·4 kcal/mole), (VIIIb) (−26·5 kcal/mole), *trans*-di*iso*propylethylene (−26·8 kcal/mole, unpublished result) and of *trans*-di-*tert*.-butylethylene (−26·9 kcal/mole, reference 18) are all in close agreement lends further support to the conclusion that in the absence of strain, the effects of alkyl substitution are independent of the nature of the alkyl group.

[19] H. C. Brown and M. Nakagawa, *J. Amer. Chem. Soc.* 77, 3610 (1955); H. C. Brown and I. Moritani, *Ibid.* 77, 3623 (1955).

The strain in (V) resulting from the opposition of *cis*-methyl and *tert.*-butyl groups is therefore sufficient to account for the relative stabilities of (IV) and (V) without recourse to the suggestion of Hughes *et al.*

In 1957 Brown *et al.*[20] reported the results of an investigation of the rates of solvolysis of phenyldimethylcarbinyl chlorides carrying alkyl substituents in the *ortho*, *meta* and *para* positions (cf. (IX)). The *para*-substituted derivatives show marked



(IX)

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acceleration in rate of solvolysis over that observed for the parent compound (IX: R = H), despite the presence of an intervening phenyl group and of two methyl groups attached directly to the center of developing electron deficiency. The ratios of rates for the substituted products to that of the unsubstituted derivative are: for *p*-methyl, 26·0; *p*-ethyl, 22·0; *p-iso*propyl, 18·8; and for *p-tert.*-butyl, 14·4. Since *meta* substitution by the same groups produces only about a two-fold acceleration, it is concluded that the *para* effect is predominantly of hyperconjugative rather than of inductive origin and further that C–C hyperconjugation is nearly as effective as C–H hyperconjugation in stabilizing an incipient carbonium ion. Comparison of the free energies of activation for the various reactions leads to values of about 0·5 kcal and 0·4 kcal for the respective contributions of hyperconjugated C–H and C–C bonds to the stability of the transition state.

In this connection thermodynamic information on related neutral molecules would be of considerable interest. The only pertinent data that appear to be available relate to the heats of combustion of *m*-methylstyrene and of *p*-methylstyrene, which are reported[1] as −1163·06 and −1162·86 kcal/mole (vapor phase, 25°), respectively. Calculation of the heat of combustion of a hypothetical methylstyrene, devoid of possible interaction between the methyl and vinyl groups, from the heat of combustion of styrene (−1018·83 kcal/mole) and the difference between the heats of combustion of toluene (−901·50 kcal/mole) and of benzene (−757·52 kcal/mole)[1] gives a comparison value of −1162·8 kcal/mole. Assuming a calorimetric precision of the order of 0·01 per cent, it follows that, within the limits of experimental error, interaction between the methyl and vinyl groups in this system is absent. The result suggests that hyperconjugation is much less important in neutral molecules than it is in electron-deficient states. The rather large stabilization observed in propylene and the lack of such in *p*-methylstyrene may, of course, be attributable to dissipation of the interaction in the benzene ring in the latter compound. The evidence is, however, not inconsistent with Dewar's hypothesis.[13] *m*-Methylstyrene and *p*-methylstyrene possess equal numbers of equivalent bonds, and the hybridization change necessary for construction of the hypothetical model (s–$sp^2 \rightarrow sp^3$–sp^2) is accounted for in the toluene–benzene difference.

The thermochemical data discussed in this paper provide strong evidence for the stabilizing influence of alkyl substituents in many unsaturated systems. That the cumulative effect is large is indicated by the difference of 6·2 kcal/mole between the

[20] H. C. Brown, J. D. Brady, M. Grayson and W. H. Bonner, *J. Amer. Chem. Soc.* **79**, 1897 (1957).

heats of hydrogenation of ethylene and tetramethylethylene. This value is comparable in magnitude to the enthalpy differences between *cis*- and *trans-cyclo*octene (9·2 kcal/mole),[21] and between *cis*- and *trans*-di-*tert*.-butylethylene (−9·3 kcal/mole),[18] which result from the involvement of severe steric strains. It is clear, however, that the calorimetric results furnish little information on the origins of the stabilization phenomenon, the nature of which must hence be sought in evidence derived from other sources.

[21] R. B. Turner and W. R. Meador, *J. Amer. Chem. Soc.* **79**, 4133 (1957).

Tetrahedron, 1959, Vol. 5, pp. 135–142. Pergamon Press Ltd. Printed in Great Britain.

SUBSTITUENT EFFECTS ON HYPERCONJUGATION: EVALUATION OF HYPERCONJUGATION ENERGY FOR GROUPS OF THE TYPE $\cdot CH_2X$

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QUALITATIVE assessment of the relative magnitudes of the mesomeric hyperconjugation of groups of the type $\cdot CH_2X$, when X is varied, was attempted[1] by a study of the equilibria:

$$p\text{-}XCH_2 \cdot C_6H_4 \cdot CH{:}O + HCN \underset{k_2}{\overset{k_1}{\rightleftharpoons}} p\text{-}XCH_2 \cdot C_6H_4 \cdot CH(OH) \cdot CN$$

whence, from the value of $K = k_2/k_1$, the values of $\Delta F = -RT \ln K$ were determined. As defined, ΔF is the increase in free energy for the dissociation of the cyanohydrin into aldehyde and hydrogen cyanide. This free-energy change will include contributions from both polar (inductive) and mesomeric ($+M$) hyperconjugative effects of the substituent group CH_2X towards the stabilisation of the free aldehyde relative to its cyanohydrin. The difficulty in the interpretation of the results arose from the inability to separate the magnitudes of the inductive and hyperconjugative components. The inductive effect of a group R is essentially a measure of the ground-state change in polarity of a C–R bond relative to that of a C–H bond as standard and, as a first approximation, this should vary little from system to system. The hyperconjugative effect may, like any conjugative effect, vary in magnitude from system to system and it depends on the degree of electron-orbital overlap and so on the extent of the conjugated system involved, i.e., on the degree of possible electron delocalisation.

Separate evaluation of the inductive and conjugative contributions would thus give more reliable information regarding the hyperconjugative effects of a single H–C bond for various groups in a given system, or of any one group in different systems. A basis for such quantitative separation has recently been provided by the treatment developed by Taft,[2] who has shown the wide application of the relationships ΔF (for equilibria) or $\log (k_R/k_H)$ (for reaction velocities) $= \sigma^*_R \rho^* + nh$, where σ^*_R is the polar constant for the substituent R (determined from a wide range of data on ester hydrolysis), ρ^* is a reaction constant which measures the susceptibility of the reaction to polar effects, n is the number of hyperconjugated C–H bonds and h is the energy associated with a single H–C bond hyperconjugation.

Application of this treatment to the earlier results for the cyanohydrin reaction makes possible some degree of quantitative evaluation of h for different groups CH_2X.

[1] J. W. Baker, J. A. L. Brieux and D. G. Saunders, *J. Chem. Soc.* 404 (1956).
[2] For a summary see R. W. Taft, Jr., *Separation of Polar, Steric, and Resonance Effects in Reactivity* in *Steric Effects in Organic Chemistry* (Edited by M. S. Newman) p. 556 *et seq.* Wiley, New York (1956).

Its application to certain reaction velocities also provides some indication of the effective hyperconjugation of alkyl groups in reactions of different polar requirements.†

In the evaluation of σ^*_R values Taft used the methyl compound as the reference standard, assigning to it the value $\sigma^*_{CH_3} = 0{\cdot}000$. On this scale hydrogen, which is less electron repelling than methyl, has $\sigma^*_H = +0{\cdot}490$. Since, in the systems here considered, the parent unsubstituted compound has been taken as the reference standard, the value of σ^*_H has been taken as 0·000, and Taft's values have been adjusted accordingly, e.g., $\sigma^*_{CH_3} = -0{\cdot}490$. *All* σ^* *values used in this paper refer to* $\sigma^*_H = 0{\cdot}000$. The treatment is first applied to cyanohydrin equilibria with *para*-alkyl-substituted benzaldehydes.

Equilibria

(a) *Alkyl groups.* The relevant data[3] for the equilibria between *p*-alkylbenzaldehydes and their cyanohydrins are in Table 1.

TABLE 1. EQUILIBRIUM CONSTANTS $K = k_2/k_1$ AND ΔF FOR THE EQUILIBRIA $p\text{-R}\cdot C_6H_4\cdot CH{:}\,O + HCN \underset{k_2}{\overset{k_1}{\rightleftharpoons}} p\text{-R}\cdot C_6H_4\cdot CH(OH)\cdot CN$ IN CONSTANT-BOILING ALCOHOL AT 20°

R	σ^*_R‡	10^2K (mole/l.)	ΔF observed (kcal)	ΔF calculated (kcal)	h (kcal)
H	0·000	4·47	3·15	(3·15)	—
CH_3	−0·490	8·98	2·75	2·75	0·07
C_2H_5	−0·590	8·18	2·80	2·78	0·062
iso-C_3H_7	−0·680	8·04	2·81	2·82	0·082
tert.-C_4H_9	−0·790	7·49	2·85	(2·85)	—

‡ Ref. 2, p. 619.

† After this treatment was completed later work by Taft suggested that σ^* values are valid indications of the magnitudes of the inductive effects of groups *only* in the aliphatic series, and he developed a treatment of equilibria and reaction velocities in aromatic systems on the basis of σ_I values, defined by the relationship $\sigma_I = 0{\cdot}45\sigma^*_{CH_2R}$, for the substituent group R. Use of σ_I values, with the corresponding reaction constants ρ_I, evaluate the inductive polar effects of *ortho*-, *meta*- or *para*-substituent groups in aromatic systems, using the relationship $1{\cdot}(1 - \alpha)[\log(K_m/K_0) - \alpha\log(K_p/K_0)] = \sigma_I\rho_I$, where α is the (constant) fraction of the resonance effect of the substituent in the *para* position which operates as a second-order effect from the *meta* position. The values of the ratio of σ^*/σ_I differ widely for different groups, and it is evident that there is, at present, no consistent relationship between σ^* and σ_I values. Moreover, the present writer finds it difficult to accept that the magnitude of the inductive effect of a group R in the system $R\text{–}C_{arom}$ should be only approximately 45 per cent of that of the group $R\cdot CH_2$ in $R\cdot CH_2\text{–}C_{alip.}$ If a damping effect to about one-third is assumed for the intercalation of the saturated methylene group, this would imply that the magnitude of the inductive effect in $R\text{–}C_{arom.}$ is only approximately 15 per cent of that in $R\text{–}C_{alip.}$ In spite of the wide correlation effected by Taft using the $\sigma_I\rho_I$ relationship, it was decided to use σ^* values (which are available for all but one of the groups studied in the cyanohydrin reaction) derived from aliphatic reactions, as probably valid empirical assessments of the relative inductive contributions to the cyanohydrin equilibria. Almost the only other *variable* polar factor in the substituted benzaldehyde system studied is the degree of hyperconjugation, and the main purpose in this paper is to obtain some relative, empirical numerical values for this contribution. Any C–C hyperconjugation has been neglected, but there is some evidence (see below) that it is not significant in the equilibria studied. The writer understands from Professor Taft (personal communication) that his alternative treatment, using the σ_I/ρ_I relationship, applied to the cyanohydrin data, does not alter any of the conclusions reached in this paper, although it gives somewhat higher numerical values for h.

[3] J. W. Baker and M. L. Hemming, *J. Chem. Soc.* 191 (1942).

The reaction proportionality constant may be evaluated by elimination of h between the various equations $\Delta F_R - \Delta F_H = (\sigma^*_R - \sigma^*_H)\rho^* - nh$. The value so obtained (+0·372) is almost identical with that obtained by assuming that C–C hyperconjugation of the *tert.*-butyl group is insignificant in these equilibria, whence, since C–H hyperconjugation is absent in both the unsubstituted and *tert.*-butylbenzaldehydes, $\Delta F_{Bu^t} - \Delta F_H = -0{\cdot}30 = -0{\cdot}790\rho^*$, i.e., $\rho^* = +0{\cdot}380$. The positive value of ρ^* is in harmony with the experimental finding that the equilibrium is displaced in the direction of the cyanohydrin by unequivocal electron attraction (e.g., $10^3K_{m\text{-}NO_2} = 2{\cdot}1$; $\Delta F = 3{\cdot}31$ kcal) and towards the free aldehyde by electron release (e.g. $10^3K_{m\text{-}CH_3} = 5{\cdot}5$; $\Delta F = 3{\cdot}03$ kcal). The values of h in the last column of Table 1 are determined from the relationships $\Delta F_R - \Delta F_H = +0{\cdot}380\ (\sigma^*_R - \sigma^*_H) - nh$†, the mean value being $h = 0{\cdot}072$. Use of this mean value assumes (with Taft) that, in this *alkyl* series of substituents, the hyperconjugation energy per H–C bond is approximately constant, an assumption which, as is shown below, is not correct when X in $\cdot CH_2X$ is not alkyl.

In order to apply the correlation not to differences in ΔF but to the individual ΔF values themselves, it is necessary to evaluate the contribution (x) due to polar and conjugative interaction of the phenyl and aldehyde groups, present in all cases. This can be done by using the unsubstituted compound in which hyperconjugation is absent and the polar effect of R = H is, by definition, zero, i.e., $3{\cdot}15 = 0{\cdot}380x$, whence $x = 8{\cdot}29$ kcal. Taft's σ^* values (polar electron attraction) for C_6H_5 and CH:O, corrected to the standard $\sigma^*_H = 0{\cdot}000$ are, respectively +0·11 and +0·86, and the extra resonance energy associated with benzaldehyde is 7·1 kcal;[4] the combined polar and resonance effects of $C_6H_5 \cdot CH{:}O$ in the parent system would thus be of the order $7{\cdot}1 + 0{\cdot}97 = 8{\cdot}07$, a value in fair agreement with that determined by the above treatment. The ΔF values for the various cyanohydrin equilibria are then accurately represented by the equation $\Delta F = 0{\cdot}380\ (\sigma^*_R + 8{\cdot}29) - 0{\cdot}072n$, or its alternative form, $\Delta F = 0{\cdot}380\ \sigma^*_R + 3{\cdot}15 - 0{\cdot}072n$, whence the calculated values of ΔF in the fifth column of Table 1 are derived. In the former expression the total polar effects of the phenyl and the aldehyde groups are regarded as subject to the reaction constant $\rho^* = 0{\cdot}380$, whilst in the latter their constant contribution, assessed from the experimental data for the unsubstituted benzaldehyde, $\Delta F = 3{\cdot}15$ kcal/mole, is separately enumerated.

Although too much significance should not be attached to the actual numerical value of h, its small value indicates the order of magnitude of the $+M$ effect of hyperconjugation per H–C bond in the equilibria studies. Thus in *p*-tolualdehyde the extra stabilisation of the free aldehyde relative to its cyanohydrin due to methyl-group hyperconjugation is only of the order of a few hundred cal/mole.

(b) *Groups of the type* $\cdot CH_2X$. The apparent validity of the above-deduced relationship for ΔF for all alkyl substituents studied suggests that it may be used to evaluate the relative values of h in the various substituent groups $\cdot CH_2X$, derived from similar data which were obtained by Baker *et al.*,[1] n in all cases (except X = H) being 2. The necessary data and results are in Table 2.

† The sign of nh is negative because, with ρ^* positive, hyperconjugation electron release will increase K, i.e., decrease ΔF. When ρ^* is negative, the sign of nh will be positive, the value of h always being assigned a positive value.

[1] M. M. Krevoy and R. W. Taft, Jr., *J. Amer. Chem. Soc.* **79**, 4016 (1957).

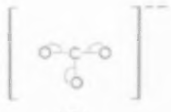
TABLE 2. EVALUATION OF MESOMERIC h FOR GROUPS CH_2X IN THE EQUILIBRIA $p\text{-}XCH_2 \cdot C_6H_4CHO + HCN \rightleftharpoons p\text{-}XCH_2 \cdot C_6H_4 \cdot CH(OH) \cdot CN$ FROM THE RELATION $\Delta F = 0{\cdot}380\ \sigma^*_R + 3{\cdot}15 - nh$

X	ΔF (kcal)	$\sigma^*_{CH_2X}$	h (kcal)
$\overset{+}{N}Et_3$†	2·55	+1·41	0·57
Cl	2·79	+0·56	0·29
HO_2C	2·92	+0·56	0·22
$(\bar{O}_2C$	2·74	?	?)
OH	2·84	+0·06	0·17
EtO_2C	3·06	+0·22	0·09
H	2·75	−0·490	0·07
CH_3	2·80	−0·590	0·06
$(OCH_3$-*p*	3·24	+0·03	−0·04)
$(OCH_3$-*m*	3·26	+0·03	−0·05)

† σ^*_R Value for $CH_2 \cdot \overset{+}{N}Me_3$ used.

With the exceptions of X = OH and OMe (discussed below) the groups CH_2X are arranged, in Table 2, in order of decreasing values of σ^*, i.e., of decreasing $-I$ effects (or increasing $+I$) and the effective hyperconjugation per H–C bond in these groups decreases from the top to the bottom of the table, in agreement with the qualitative order previously postulated.[1] This semi-quantitative treatment of the equilibria thus confirms the earlier suggestion[1] that hyperconjugation of $-CH_2X$ is increased by the capacity of the group X to stabilise the negative charge in the canonical structure $X \cdot \overset{\overset{+}{H}}{\bar{C}}H \cdot C_6H_4 \cdot CH{:}O$, involved in hyperconjugation, and thus to increase the importance of such structures in the mesomeric structure of the aldehyde. Such stabilisation may be by either inductive or conjugative effects of X. Stabilisation by the inductive effect ($-I$) is illustrated by the observation that the value of h for CH_2X decreases in the order $X = \overset{+}{N}Et_3 > Cl > OH$, which is the order of decreasing $-I$ effects of X. Stabilisation by the conjugative effect of X is illustrated by the cases where $X = CO_2Et$, CO_2H and $CO \cdot \bar{O}$, all of which show a greater degree of hyperconjugation, per H–C bond, than when X = H. It is unfortunate the σ^* values are not available for the group $CH_2 \cdot \bar{C}O_2$, and hence it is not possible to get any quantitative assessment of the contribution of inductive electron release towards the relative stabilisation of the free aldehyde, but it may be noticed that the structure $\bar{O} \cdot CO \cdot \overset{\overset{+}{H}}{\bar{C}}H \cdot C_6H_4 \cdot CH{:}O$, in which the two negative charges may be distributed between two oxygen atoms and the formylbenzyl group (*A*), simulates very closely the resonance stabilisation in the symmetrical carbonate anion (*B*).

(A)



(B)

One other factor may possibly make a small contribution when X is strongly electron attracting. Before the experimental results were obtained Coulson (personal communication) made a very tentative guess that increase in the electron-attracting power of X would cause a flow of charge in the C–X bond, leading to increased electronegative character of the carbon atom. This should make the CH_2 group a little more coplanar with the phenyl ring and so facilitate hyperconjugation, but the effect, if present, would be very small. The conformity of the experimental results with this conclusion may indicate that it is a factor which makes a small contribution towards the increased hyperconjugation observed when X is a strongly electron-attracting group like $\overset{+}{N}R_3$.

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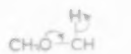
The group $CH_3O \cdot CH_2$ is anomalous, since the values of ΔF for the *meta*- and *para*-substituted derivatives are almost identical, indicating the absence of any significant conjugative effect. The meaningless very small negative values for h found with this group confirm this conclusion. One possible explanation might be found in competing *anionic* hyperconjugation,[5]



but the different behaviour of the groups $HO \cdot CH_2$– and $CH_3O \cdot CH_2$– is difficult to explain on this basis.

Velocity data

In reaction velocities, all polarizability effects, favourable to the reaction, will be called into play. These may include inductomeric and electromeric effects and all such effects will be included, indiscriminately, in any conjugative or hyperconjugative effect derived from the application of the $\sigma^*\rho^*$ type of analysis. For this reason alone, similar analysis of velocity data may not be quite as satisfactory as a means of evaluating the hyperconjugation contribution, but such analyses do, nevertheless, provide some interesting results.

(a) *In the cyanohydrin reaction.* Baker and Hemming[3] also determined the separate values of k_1 and k_2 in the benzaldehyde–cyanohydrin reaction. Their results are in Table 3. These are less accurate than are those for the equilibrium constants K, especially those for k_2, which were determined from the relation $k_2 = k_1K$ and so involve the product of the separate experimental errors in both K and k_1. These k_2

TABLE 3. VELOCITY DATA FOR THE REACTION p-R · C_6H_4 · CHO + HCN $\underset{k_2}{\overset{k_1}{\rightleftharpoons}}$ p-R · C_6H_4 · CH(OH) · CN IN EtOH OF CONSTANT BOILING POINT AT 20°

R=	H	CH_3	C_2H_5	*iso*-C_3H_7	*tert.*-C_4H_9
10^2k_1 (mole^{-1}l. sec^{-1})	1·96	0·98	1·01	0·85	0·91
log (k_1^R/k^H)	0	−0·301	−0·288	−0·363	−0·333
$10^{10}k_2$ (sec^{-1})	0·87	0·88	0·82	0·68	0·68
σ^*_H	0·00	−0·490	−0·590	−0·680	−0·790

[5] F. H. Seubold, Jr., *J. Org. Chem.* **21**, 156 (1956).

values do not conform to the above analytical treatment. An approximate treatment of the k_1 values is, however, possible, although even here the very small velocity differences do not readily lend themselves to such analysis.

Although the values of h vary slightly for the different alkyl substituents (0·03, 0·02, 0·07), these results are approximately represented by the relationship $\log (k_1^R/k_1^H) = +0{\cdot}43\sigma^*_R - 0{\cdot}03n$. The rather larger positive value for ρ^* for the forward reaction than for the equilibrium is in agreement with Lapworth's early finding[6] that, in cyanohydrin formation, attack is by the $\bar{C}N$ ion and hence the forward reaction is facilitated by electron attraction away from the carbonyl carbon atom. The small value of h, of the same order of magnitude as that in the equilibrium expression, suggests that only the mesomeric component ($+M$) of hyperconjugation is operative in the forward reaction, a conclusion to be expected since hyperconjugation is an electron-release mechanism which would retard the electrostriction of the cyanide ion.

(b) *In unimolecular* (S_N1) *and bimolecular* (S_N2) *nucleophilic substitution.* In the unimolecular nucleophilic substitution, the solvolysis of benzhydryl chlorides,[7] the rate-determining stage $p\text{-R} \cdot C_6H_4 \cdot CHPh\text{–}Cl \rightarrow p\text{-R} \cdot C_6H_4 \cdot \overset{+}{C}HPh + \bar{C}l$, is unequivocably facilitated by electron release by the group R = alkyl and hence the mesomeric hyperconjugation ($+M$) will here be greatly increased by the operation of a strong electromeric component ($+E$). Application of the above method of analysis should thus reveal the magnitude of this total H–C hyperconjugative effect. The relevant data, including some later results of Shiner and Verbanic,[8] are in Table 4.

TABLE 4. VALUES OF k_1 FOR THE SOLVOLYSIS OF $p\text{-R} \cdot C_6H_4 \cdot CHPhCl$ IN 80 PER CENT AQUEOUS ACETONE AT 0°

R	σ^*_R	$10^6 k_1$	$\log k_1^R/k_1^H$†	h
H	0·000	2·82[7]; 2·618[8]	0	—
CH_3	−0·490	83·5	+1·4715[7]	0·26
C_2H_5	−0·590	62·6	+1·3464[7]	0·26
iso-C_3H_7	−0·680	47·0	+1·2219[7]	0·27
tert.-C_4H_9	−0·790	35·9	+1·1049[7]	—
n-C_3H_7	−0·620	56·92	+1·3374[8]	0·23
$(CH_3)_2CH \cdot CH_2$	−0·615	50·2	+1·2828[8]	0·21
$(CH_3)_3C \cdot CH_2$	−0·655	40·06	+1·1848[8]	0·13

† With reference to value of $\log k^H$ observed by the particular investigator.

Solution of the various equations $\log (k_1^R/k_1^H) = \sigma^*_R\rho^* + nh$ gives $\rho^* = -1{\cdot}40$, whence the various values of h in the last column of Table 4 are determined. For the results of Hughes *et al.*[7] this unimolecular solvolysis is accurately represented by the relation $\log (k_1^R/k_1^H) = -1{\cdot}40\sigma^*_R + 0{\cdot}26n$; those of Shiner and Verbanic require a slightly smaller value for h. The large negative value of ρ^* indicates the expected strong *facilitation* of this reaction by electron release from R and the much larger

[6] A. Lapworth, *J. Chem. Soc.* **83**, 995 (1903).
[7] E. D. Hughes, C. K. Ingold and N. A. Taher, *J. Chem. Soc.* 949 (1940).
[8] V. J. Shiner, Jr. and Verbanic, *J. Amer. Chem. Soc.* **79**, 369 (1957).

value of h (approximately 0·26) indicates that the total ($+M$, $+E$) hyperconjugative effect per H–C bond now operative is at least four times as great as the mesomeric component alone. The significantly lower value of h for the *neo*pentyl group may well indicate some steric inhibition of the hyperconjugation[9] in addition to the $+I$ effect of the substituent CMe_3 group on the effective hyperconjugation of the attached CH_2 group.

The bimolecular nucleophilic substitution:

$$p\text{-R} \cdot C_6H_4 \cdot CH_2Br + C_5H_5N \rightarrow p\text{-R} \cdot C_6H_4 \cdot CH_2 \cdot \overset{+}{N}C_5H_5\}\overset{-}{Br},$$

from the results of which the concept of H–C hyperconjugation was originally formulated,[10] will be much less electron demanding, since, in the transition state, electron release, although facilitating the separation of bromine with its bonding electrons, will hinder the electrostriction of the pyridine molecule. Hyperconjugative electron release should thus be much smaller. Analysis of the experimental results, given in Table 5, completely confirms both these conclusions.

TABLE 5. VALUES OF k_2 FOR THE REACTION

$p\text{-R} \cdot C_6H_4 \cdot CH_2Br + C_5H_5N \rightarrow p\text{-R} \cdot C_6H_4 \cdot CH_2 \cdot \overset{+}{N}C_5H_5 + \overset{-}{Br}$

IN DRY ACETONE AT 20°

R	σ^*_R	$10^4 k_2$ (mole^{-1}l. sec^{-1})	log (k_2^R/k_2^H)	h
H	0·000	1·22	0	—
CH_3	−0·490	2·02	+0·2190	0·049
C_2H_5	−0·590	1·81	+0·1693	0·040
iso-C_3H_9	−0·680	1·63	+0·1258	0·024
tert.-C_4H_9	−0·790	1·65	+0·1311	—

The relative velocity data are represented by the equation log $(k_2^R/k_2^H = -0{\cdot}15\sigma^*_R + 0{\cdot}04n$ to an accuracy of 0·01 − 0·02 log units. The much smaller negative value of ρ^* reflects the smaller electron demand of this S_N2 reaction. The low value of h, of the same order of magnitude as that for the mesomeric component, suggests that the polarisation of the C–Br bond in the transition state

$$C_5H_5\overset{\delta+}{N}\cdots\underset{|}{CH_2}\cdots\overset{\delta-}{Br}$$

does not invoke appreciable unsaturation at the methylenic carbon atom to stimulate any electromeric hyperconjugative effect.

Too much significance must not be attached to the absolute numerical values of h, but these analyses, based on free-energy calculations, suggest that the energy associated with the mesomeric hyperconjugation of a single H–C bond in *alkyl* groups attached to an aromatic system is small and only about 40–70 cal/mole, whereas when the

[9] G. Baddeley, J. Chadwick and S. B. Rawlinson, *Nature, Lond.* **164**, 833 (1949); cf. G. Baddeley and M. Gordon, *J. Chem. Soc.* 2190 (1952).
[10] J. W. Baker and W. S. Nathan, *J. Chem. Soc.* 1844 (1935); J. W. Baker, *J. Chem. Soc.* 1150 (1939).

electromeric effect is stimulated by a strongly electron-demanding reaction this value is increased about four-fold to approximately 260 cal/mole. These values of h are appreciably lower than the average value (approximately 0·5 kcal) found by Taft and Kreevoy for the enthalpies of hydrogenation of various substituted ethylenes and the free energies of hydrogenation of carbonyl compounds $R^1R^2C{:}O$. They suggest that the conclusion of these authors that hyperconjugation stabilisation is less susceptible to electron demand at the reaction centre and may be assigned an approximately constant value (approximately 0·5) is possibly a somewhat oversimplified generalisation. The value and usefulness of Taft's method of analysis for the evaluation of the approximate magnitudes of hyperconjugation effects is, however, further illustrated by the analyses described in this paper.

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ISOTOPE EFFECTS AND HYPERCONJUGATION

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SEVERAL years ago the observation of an isotope effect in the decomposition of 2-pentyl chlorosulfite led to the suggestion that the isotope effect measured the increase in hyperconjugation accompanying the activation.[1] This paper examines the suggestion in the light of subsequent work with the aim of establishing the extent of connection between these isotope effects and hyperconjugation. There will be no attempt to use isotope effects to study the nature of hyperconjugation.

For the purposes of this paper, hyperconjugation is considered to be a contribution to the usual hybrid of valence-bond structures of reasonable further structures with no bond to some atom in place of the single bond of the conventional structures. The partial withdrawal of the electrons of a single bond to another part of the molecule where they can be accommodated is the important feature of this definition, the valence-bond language is not essential for the present purpose. We shall here be only concerned with hyperconjugation involving withdrawal of electrons from a bond to hydrogen, nothing can be said from this work about the so called C–C hyperconjugation.

It was suggested that, when electrons are withdrawn from a C–H bond by hyperconjugation, the force constants for the vibration of the hydrogen are reduced. A reaction with a change in hyperconjugation on activation would then be a process with different force constants of the C–H bond in the starting material and in the activated complex. Thus substitution of deuterium for hydrogen will produce a difference in the change of zero-point vibrational energies on activation for the deuterium and the protium compounds. This difference will in turn be reflected in different activation energies and different rates for the two compounds. When a reaction results in an increase in hyperconjugation on activation, it will be expected to involve a loss in zero-point vibrational energy which will be greater for the protium compound than the deuterium compound, hence the protium compound will react more rapidly.* On this basis it was proposed that the extent of retardation by appropriate deuterium substitution was a measure of the increase in hyperconjugation and hence the increase in electron deficiency on activation.

The initial experiments which led to these ideas were on the decomposition of 2-pentyl chlorosulfite in dioxan solution to a mixture of pentenes and 2-chloropentane. Nearly complete deuteration in the 1 and 3 positions produced a diminution in the

* This simple treatment makes a number of assumptions about the sources of isotope effects which are only approximate. It can be shown for the cases mentioned here that errors resulting from these assumptions are not serious except when the isotope effect is small, but with $k_H/k_D < 1{\cdot}1$ a more complete treatment would be better if it could be applied.

[1] E. S. Lewis and C. E. Boozer, *J. Amer. Chem. Soc.* **74**, 6306 (1952); *Ibid.* **76**, 795 (1954).

rate of both reactions with k_H/k_D = ca. 1·4. Both processes were believed to proceed through the rate-determining formation of an ion-pair:

$$ROSOCl \longrightarrow R^+ \quad OSOCl^-$$

It was desirable to determine an isotope effect on a reaction of well-established mechanism, so the solvolysis of 2-pentyl *p*-toluenesulfonate, in which a transition state closely resembling a carbonium ion is accepted, was chosen.[2] Before this was complete, a very important and pertinent paper by Shiner[3] appeared describing a corresponding diminution in solvolysis rate of *tert.*-amyl chloride produced by β-deuterium substitution. Table 1 shows some of the results of our work and confirms the ideas that this isotope effect occurs in reactions leading to carbonium ions. The rate retardations are expressed at times in this paper as k_H/k_D and elsewhere as (RT/n) ln k_H/k_D, where n is the number of deuteriums per molecule in positions suitable for hyperconjugation. The latter mode of expression is useful for comparing isotope effects at different temperatures and with different numbers of deuterium atoms. In the case of the first two entries in the table it was shown that the free energy of activation difference was indeed temperature independent, showing that the difference occurred exclusively in the heat of activation term. The justification for expressing the effect on the basis of the $\Delta\Delta F^{\ddagger}$ per deuterium is found in the work of Shiner[3] and that of Streitwieser *et al.*,[4] both of whom have shown that the effect of deuterium substitution on the rate is nearly independent of the presence of other deuterium atoms in the molecule. There are, however, well established cases where the effect of deuterium depends on the extent of substitution of the carbon to which it is attached,[3, 5] and where deuterium substitution produces changes in the Arrhenius pre-exponential factor.[5, 6]

TABLE 1. ISOTOPE EFFECTS IN SOLVOLYSIS OF 2-PENTYL COMPOUNDS

Substance	Solvent	$(RT/n)\ln k_H/k_D$ (cal/mole)
ROTs	HCOOH	76
ROTs	CH_3COOH	75
ROTs	80% EtOH	51
RBr	HCOOH	56

Table 1 shows the fall in isotope effect as the solvent or leaving group becomes more nucleophilic, hence supporting the suggestion that the less electron-deficient transition state leads to a smaller isotope effect. Table 2 shows the decrease in isotope effect as we proceed from the limiting tertiary halide, which does not need solvent participation, through the intermediate secondary compound to the primary ethyl compound, where the electron-deficient carbonium ion is a very poor description of the transition

[2] E. S. Lewis and C. E. Boozer, *J. Amer. Chem. Soc.* **76**, 791 (1954).
[3] V. J. Shiner, Jr., *J. Amer. Chem. Soc.* **75**, 2925 (1953).
[4] A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey and S. Suzuki, *J. Amer. Chem. Soc.* **80**, 2326 (1958).
[5] V. J. Shiner, Jr., *J. Amer. Chem. Soc.* **76**, 1603 (1954).
[6] E. S. Lewis and G. M. Coppinger, *J. Amer. Chem. Soc.* **76**, 4495 (1954).

state. The parenthesized value for the 2-pentyl bromide in 80 per cent ethanol is estimated from Table 1.

TABLE 2. STRUCTURAL INFLUENCE ON ISOTOPE EFFECT WITH NEARLY COMPLETE β-DEUTERIUM SUBSTITUTION

Compound	Solvent	$(RT/n)\ln k_H/k_D$ (cal/mole)
tert.-Amyl chloride	80% EtOH	55[8]
2-Pentyl bromide	80% EtOH	(37)
2-Pentyl *p*-toluenesulfonate	CH_3COOH	75
Ethyl *p*-bromobenzenesulfonate	CH_3COOH	6[7]

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A simple extension of these ideas requires that the isotope effect in the ordinary S_N2 reaction should be very small, since the contribution of hyperconjugating electron-deficient structures is minor. Two examples have been studied. The reaction (1) with

$$OEt^- + RBr \longrightarrow EtOR + Br^- \qquad (1)$$

R = *iso*propyl was studied by Shiner [8] and shows a very small and possibly experimentally insignificant isotope effect, with $(RT/n)\ln k_H/k_D = 12$ cal/mole. The reaction of 2-pentyl chlorosulfite in the presence of tertiary amines is an inverting chloride ion substitution represented by (2), it has $(RT/n)\ln k_H/k_D = 35$ cal/mole.[9] Both numbers are substantially smaller than those for any analogous S_N1 reactions.

$$Cl^- + ROSOCl \longrightarrow ClR + SO_2 + Cl^- \qquad (2)$$

The connection between retardation by β deuterium and the carbonium-ion character of the transition state is now reasonably well established, but the results described above do not necessarily identify hyperconjugation as the mechanism of this connection. Most alternative explanations, not involving conjugation, would not predict transmission of the effect through an unsaturated system, so the solvolysis of methyltolylcarbinyl chlorides were studied. Table 3 shows the effects of deuterium substitution in various positions on the solvolysis rates of methyl-*p*-tolylcarbinyl chloride in acetic acid[6] and of this substance and the *meta* isomer in aqueous acetone.[10] Variations of isotope effect with temperature and with the composition of aqueous acetone are not shown. Since the effects are small, the significance of these variations is questionable.

Four features are evident from these data. First, deuterium in the *para*-methyl group does cause some retardation; second, this isotope effect is subject to large changes with solvent; third, deuterium in the *meta*-methyl group does not cause a retardation, and indeed appears to lead to an increased rate; fourth, deuterium in the α position produces a large retardation.

The first of these, retardation by deuterium in the *para*-methyl group, lends support to an explanation in terms of hyperconjugation, especially when the retardation

[7] E. S. Lewis and W. C. Herndon, unpublished work.
[8] V. J. Shiner, Jr. *J. Amer. Chem. Soc.* **74**, 5285 (1952).
[9] E. S. Lewis and G. M. Coppinger, *J. Amer. Chem. Soc.* **76**, 796 (1954).
[10] R. R. Johnson, Thesis, the Rice Institute, Houston, Texas (1958).

TABLE 3. ISOTOPE EFFECTS IN THE SOLVOLYSIS OF METHYLTOLYLCARBINYL CHLORIDES

Position of D	Tolyl isomer	Solvent	k_H/k_D
p-CH_3	*para*	CH_3COOH	1·08
ω-CH_3	*para*	CH_3COOH	1·2
p-CH_3	*para*	Me_2CO–H_2O	1·01
ω-CH_3	*para*	Me_2CO–H_2O	1·13
α-CH	*para*	Me_2CO–H_2O	1·11
m-CH_3	*meta*	Me_2CO–H_2O	0·99

is not found with the *meta* isomer. A difference in direction of effect in the *meta* and *para* position is always difficult to explain without recourse to a resonance, or in this case hyperconjugation, effect. The effect in aqueous acetone is very small, but, since the precision of the rate constants was good, it is significant. Shiner and Verbanic[11] have observed a similar effect with *p*-methylbenzhydryl chloride.

The second point, the solvent dependence, is quite interesting. The solvent change shown in Table 3 is in the direction predicted by the considerations of solvent participation mentioned before, but the large change in isotope effect due to the deuterium in the *para*-methyl group is not compatible with the relatively minor change in isotope effect due to substitution in the other methyl group, marked ω in the table. Shiner and Verbanic[11] also observed substantial solvent effects over a small solvent variation. Both results are consistent with solvent participation at some other point than at the electron-deficient carbon, but the details are not clear.

The acceleration by deuterium in the *meta*-methyl group is quite unprecedented. An explanation in terms of an inductive effect can be offered and will be discussed in more detail later.

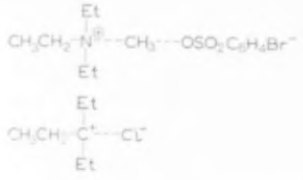
The effect of α deuterium is clearly not related to hyperconjugation. It is included to demonstrate that there are other sources of secondary isotope effects. The first example was found by Streitwieser *et al.*,[4] who have offered a reasonable explanation.

An interesting extension of these experiments on the aromatic systems is found in the decomposition in water of the *p*-toluenediazonium ion. This substance is stabilized by important hyperconjugation, but the immediate product of the reaction, the *p*-tolyl cation, is not so stabilized. This is deduced from the observation that a *para*-methyl group stabilizes the diazonium ion with respect to this reaction, but the *meta*-methyl group reduces its stability. Thus the inductive effect of the methyl group favors the reaction, and the diminished reactivity of the *para*-methyl substituted compound must be attributed to a resonance effect.[12] One therefore predicts that the C–H bonds of the CH_3 group will be stronger in the transition state than in the initial state, hence substitution of deuterium will lead to an acceleration. The observation[13] that $k_H/k_D = 0{\cdot}99$ is positive, if not convincing, confirmation of this prediction.

Inductive differences between hydrogen and deuterium have been proposed by Halevi[14] in the direction of greater electron release by deuterium than by hydrogen.

[11] V. J. Shiner, Jr. and C. J. Verbanic, *J. Amer. Chem. Soc.* **79**, 373 (1957).
[12] E. S. Lewis and E. B. Miller, *J. Amer. Chem. Soc.* **75**, 429 (1953).
[13] E. S. Lewis, J. L. Kinsey and R. R. Johnson, *J. Amer. Chem. Soc.* **78**, 4294 (1956).
[14] E. A. Halevi, *Tetrahedron* **1**, 174 (1957).

He arrived at this conclusion from considerations of differences in acid strength between phenylacetic acid and its α-dideutero analogue. Benzylamine and its α-dideutero analogue similarly differed in base strength. The source of this difference was attributed to the difference in CH and CD bond distances; the smaller distance for the latter arises in a straightforward way from considerations of zero-point vibration of the anharmonic system. Independent confirmation is found in the shielding of the fluorine nuclei in the CF_2H group of n-C_3F_7H,[15] which by nuclear magnetic resonance methods is less than the shielding by valence electrons of the corresponding nuclei in n-C_3F_7D. This inductive effect best explains the previously quoted results on the increase in rate on substitution of deuterium for hydrogen in methyl-*m*-tolylcarbinyl chloride, and (as suggested by Halevi) may also explain the reverse isotope effect in the reaction of *p*-toluene-diazonium ion. There is now additional evidence on this point from kinetic work. The reaction of methyl *p*-bromobenzenesulfonate with triethylamine has a transition state as shown below resembling that for the solvolysis of triethylcarbinyl chloride electrostatically, although in the solvolysis the atom developing the positive charge is electron deficient, and in the quarternization reaction there is no significant electron deficiency at the nitrogen. The effect of deuterium in



one methylene group of the triethylamine was to accelerate the reaction, with $k_H/k_D = 0{\cdot}93$.[16] Not only is the result most easily explained on the basis of an inductive difference, but one can also conclude that the more usual isotope effect in solvolysis is not derived from an electrostatic effect alone, since one might expect isotope effects in the same direction for the quaternization and the solvolysis if the charge near the point of isotopic substitution were the important factor.

In addition to work on solvolytic reactions, evidence relating isotope effect and hyperconjugation has come from other sources. Shiner and Cross[17] have found similar but smaller effects in the hydrolysis of acetals, where hyperconjugation had been considered important from other evidence. Swain *et al.*[18] studied the effect of tritium in the methyl group of toluene on the rate of bromination in aqueous acetic acid, and on the rates of some other electrophilic substitutions. Since the transition state for bromination was believed to be highly electron deficient, they estimated that the isotope effect should be larger than in the solvolysis reaction. The observed ($k_H/k_T = 1{\cdot}046 \pm 0{\cdot}009$) isotope effect was smaller than that reported for a solvolysis reaction,[6] so it was concluded that the isotope effect and hyperconjugation were not directly connected. Since the later results, quoted above and in reference 11, show that there is substantial variation in isotope effect with solvent, Swain's result is no longer unexpectedly low, hence his conclusion is no longer necessary. This example does

[15] G. V. D. Tiers, *J. Amer. Chem. Soc.* **79**, 5585 (1957).
[16] E. S. Lewis and W. J. Farrissey, unpublished observations.
[17] V. J. Shiner, Jr. and S. Cross, *J. Amer. Chem. Soc.* **79**, 3599 (1957).
[18] C. G. Swain, T. E. C. Knee and A. J. Kresge, *J. Amer. Chem. Soc.* **79**, 505 (1957).

illustrate the caution that it is now necessary to use in quantitative interpretation of isotope effects.

In conclusion, it may now be taken as established that hyperconjugation is one of the important sources of secondary isotope effects. There exist other sources of isotope effects, including an inductive difference and an effect from α substitution. Furthermore, the variation of solvent influences the isotope effect is a way that is not well understood, so that the quantitative use of secondary isotope effects is not a reliable tool for studying mechanisms, except when the effects are large.

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A SIMPLE MOLECULAR ORBITAL TREATMENT OF HYPERCONJUGATION*

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Abstract—A modification of the simple molecular orbital theory has been successfully applied to the treatment of ionization potentials of unsaturated molecules. Of the several models examined for the hyperconjugative effect of a methyl group, best results were obtained for a model in which the methyl group is treated as a single "heteroatom" which donates two electrons to the π system.

As part of a program to investigate the quantitative and semi-quantitative application of the simple molecular orbital theory with neglect of overlap to organic chemistry, we have examined the treatment of ionization potentials. The resulting correlation has been used in an examination of several models for a methyl group.

Ionization potentials in the simple theory

In the simple molecular orbital (Hückel) theory all of the Coulomb integrals, α_r, are taken to be the same; all of the exchange integrals, β_{rs}, for bonded atoms are taken as equal. β for non-neighboring atoms are taken as zero and all overlap integrals of the type, $S_{rs}(r \neq s)$, are taken as zero. The energy, ϵ_j, of each molecular orbital, ψ_j, is obtained in the form of equation (1):

$$\epsilon_j = \alpha + m_j\beta \tag{1}$$

The ionization potential, I, should be given by the energy of the highest occupied molecular orbital.[1] Stevenson[2] has obtained the ionization potentials of a number of polycyclic aromatic hydrocarbons by electron impact and has demonstrated for this related family of compounds an excellent correlation between the experimental ionization potentials and the corresponding energies of the highest occupied molecular orbitals. His results are summarized in Table 1 and are plotted in Fig. 1. An attempt to extend this simple treatment to other compounds fails. Although styrene fits quite well, the points for ethylene and butadiene fall far from Stevenson's correlation line. To some extent the discrepancy is due to the use of a common value for β.

The bond distances in ethylene and butadiene differ substantially from those in the aromatic hydrocarbons. Making the usual assumption that β is proportional to the overlap integral, β_{rs} for a double bond becomes 1·07 β, in which β is now the exchange integral for the C–C bond in benzene. Similarly, β_{rs} for the single bond in butadiene becomes 0·91 β. The effect of the use of these values for β_{rs} in ethylene, butadiene and styrene are shown by the crosses in Fig. 1. In the first two cases the change is too small to produce any substantial improvement in the correlation.

* This work was supported by the United States Air Force through the Air Force Office of Scientific Research of the Air Research and Development Command, under contract No. AF49(638)-105. Reproduction in whole or in part is permitted for any purpose of the United States Government.

[1] S. A. Matsen, *J. Chem. Phys.* **24**, 602 (1956).
[2] D. P. Stevenson, personal communication.

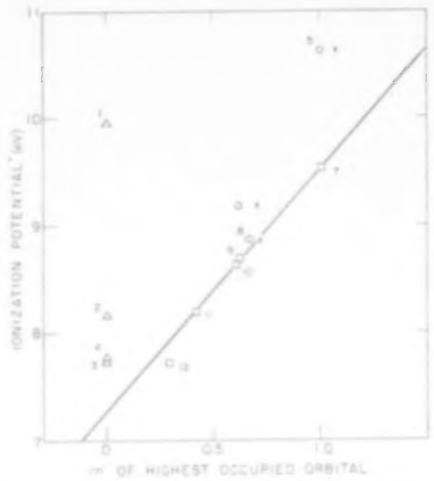

FIG. 1. Ionization potentials in the simple molecular orbital theory. Numbers correspond to compounds in Table 1.

TABLE 1. IONIZATION POTENTIALS OF SIMPLE π SYSTEMS

No.	Compound	$I_{calcd.}$ (eV)	Simple MO m_j	χ ($\omega = 1{\cdot}4$)	$I_{calcd.}$ (eV) eq. (4)	Δ ($I_{calcd.} - I_{exp.}$)
1	Methyl	9·95[4]	0	0	9·88	−0·07
2	Allyl	8·16[4]	0	0·785	8·22	0·06
3	Pentadienyl	7·73[5]	0	1·018	7·74	0·01
4	Benzyl	7·76[4, 6]	0	1·001	7·76	0·00
5	Ethylene	10·62[7]	1·000 (1·070)*	−0·370	10·66	0·04
6	Butadiene	9·18[8]	0·618 (0·708)*	0·310	9·22	0·04
7	Benzene	9·52[9, 10]	1·000	0·167	9·53	0·01
8	Styrene	8·86[5]	0·662 (0·718)*	0·445	8·94	0·08
9	Naphthalene	8·68[5]	0·618	0·592	8·63	−0·05
10	Phenanthrene	8·62[5]	0·605	0·653	8·50	−0·12
11	Anthracene	8·20[5]	0·414	0·839	8·11	−0·09
12	Naphthacene	7·71[5]	0·295	0·982	7·81	0·10

* Values of m_j for unequal β.

A further important discrepancy is found in an attempted extension of the simple treatment to radicals of the alternant hydrocarbon type.[3] In these radicals, as exem-

[3] C. A. Coulson and H. C. Longuet-Higgins, *Proc. Roy. Soc.* A **192**, 16 (1947).
[4] F. P. Lossing, K. U. Ingold and I. H. S. Henderson, *J. Chem. Phys.* **22**, 621 (1954).
[5] D. P. Stevenson, personal communication.
[6] J. B. Farmer, I. H. S. Henderson, C. A. McDowell and F. P. Lossing, *J. Chem. Phys.* **22**, 1948 (1954).
[7] R. E. Honig, *J. Chem. Phys.* **16**, 105 (1948).
[8] J. Collin and F. P. Lossing, *J. Amer. Chem. Soc.* **79**, 5848 (1957).
[9] J. D. Morrison and A. J. C. Nicholson, *J. Chem. Phys.* **20**, 1021 (1952).
[10] F. H. Field and J. L. Franklin, *J. Chem. Phys.* **22**, 1895 (1954).

plified by methyl, allyl, benzyl and pentadienyl radicals, the highest occupied molecular orbital is a singly occupied non-bonding orbital. Hence, these radicals should all have the same ionization potential according to the simple theory. Experimentally, the ionization potentials of these radicals vary over a range of more than 2 eV. The discrepancy is demonstrated in Table 1 and in Fig. 1. These results demonstrate that without modification the simple molecular orbital treatment is of limited usefulness in the correlation of ionization potentials.

Effect of α as a function of charge

The defect in the treatment of ionization potentials demonstrated above undoubtedly arises from the neglect of electron-repulsion terms in the simple theory. This problem can be handled by the use of more elaborate molecular orbital techniques; several calculations of ionization potentials by using such techniques have been reported,[11] the most extensive of which are the recent semi-empirical self-consistent molecular orbital calculations of Hush and Pople.[12] In the simple theory for families of related neutral systems the effects of electron-repulsion terms are apparently relatively constant and are absorbed in the empirical values used for the parameters, α and β. The change of a neutral system to a cation is accompanied by a decrease in electron repulsion which is not effectively constant for different systems. The net effect of a decrease in electron repulsion can be approximated by a corresponding increase in Coulomb attraction; i.e., by an increase in the effective electronegativity of appropriate atoms in the system. In the simple theory this would involve an increase in the absolute values of appropriate α's. Wheland and Mann[13] introduced the assumption that the increase in α of a carbon atom in an unsaturated cation is proportional to the positive charge on the atom. We have followed this assumption with the use of equation (2), but have treated the proportionality constant, ω, as a disposable parameter:

$$\alpha_r = \alpha_0 + \omega(1 - q_r)\beta \tag{2}$$

For each compound, the usual simple molecular orbital energy equations were set up and solved with neglect of overlap. An electron was removed from the highest occupied molecular orbital, and the resulting charge distribution was determined. Equation (2) then gave the change in the α of each carbon for each of several assumed values of ω. These α values were used to set up a new energy matrix, from which the energy of the cation was determined in the usual way. The ionization potential is then given by equation (3):

$$I = E(\text{cation}) - E(\text{hydrocarbon}) = -\alpha + \chi\beta \tag{3}$$

The use of the same values of β for the neutral hydrocarbon or radical and the cation implies that there is no change in molecular geometry during the ionization process. Hence, the calculated energy changes relate to the vertical ionization potentials such as are given by electron-impact methods. For each of several values of ω, the χ values were plotted against the corresponding experimental ionization potentials.

[11] Examples are: O. Chalvet and R. Daudel, *C.R. Acad. Sci., Paris* **235**, 960 (1952); I. Tanaka and C. Komatsu, *J. Chem. Phys.* **23**, 976 (1955); H. C. Lefkovits, J. Fain and F. A. Matsen, *Ibid.* 1690.
[12] N. S. Hush and J. A. Pople *Trans. Faraday Soc.* **51**, 600 (1955).
[13] G. W. Wheland and D. E. Mann, *J. Chem. Phys.* **17**, 264 (1949).

Best agreement was obtained for $\omega = 1{\cdot}4$. The data for this case are plotted in Fig. 2. An excellent linear correlation is obtained; the least-squares correlation line is given in equation (4), in which the uncertainties are given as the standard deviations:

$$I\,(\text{eV}) = (-2{\cdot}110 \pm 0{\cdot}050)\chi + 9{\cdot}878 \pm 0{\cdot}073 \qquad (4)$$

By using equation (4), the χ values were converted to calculated ionization potentials. These values are compared with the experimental values in Table 1. The maximum deviation is only 0·1 eV. The average deviation, 0·05 eV, is about the same magnitude as the usual experimental error. Considering the wide variety of structural

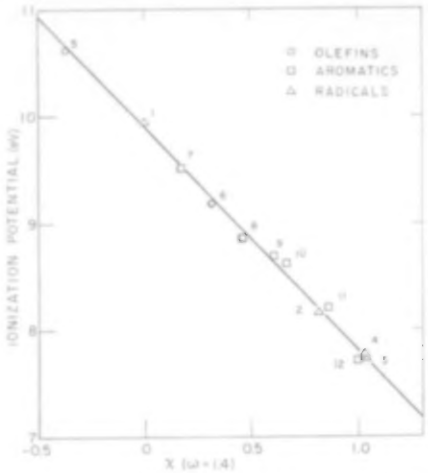

Fig. 2. Correlation of ionization potentials of simple π systems with calculated energy differences. The linear correlation is taken as the standard. Numbers correspond to compounds in Table 1

Table 2. Successive iterations for butadiene cation

No. of iterations	q_1	q_2	x
0	0·652	0·848	
1	0·729	0·771	0·310
2	0·669	0·831	0·332
3	0·716	0·784	0·312
4	0·679	0·821	0·326
5	0·708	0·792	0·314
6	0·685	0·815	0·323
7	0·703	0·797	0·316
8	0·689	0·811	0·321
9	0·700	0·800	0·317
10	0·691	0·809	0·320
11	0·698	0·802	0·318
∞	0·695*	0·805*	0·319*

* Estimated.

types involved—radicals, olefins and aromatic hydrocarbons—and the range of almost 3 eV covered, the agreement is indeed remarkable for such a crude theory.

3,4-Benzphenanthrene was not included in the standard correlation because of the possibility that the strain in this hydrocarbon might introduce anomalous effects. However, the χ value for 3,4-benzphenanthrene, 0·721, corresponds to 8·36 eV in excellent agreement with the experimental ionization potential, 8·40 eV.[5] For graphite, the value of χ equals ω, hence I (calcd.) is 6·93 eV, in poor agreement with the experimental value, 4·39 eV, quoted by Mulliken[14] for the work function of graphite.

The calculations described amount to the first iteration of a self-consistent field treatment. The resulting charge densities may be expected in general to differ from the starting Hückel charge densities. The effect of the use of ω is to spread the charge density more evenly throughout the molecule. In several cases, the effect of successive iterations was examined. The charge densities obtained from the first iteration described above were used to derive new α's, by using equation (2). The energy matrix was changed accordingly and was rediagonalized to yield new values of χ and the charge densities. This procedure could be repeated until self-consistency was obtained if the series was convergent. The results of such successive iterations applied to butadiene are given in Table 2 in which q_r is the charge density. In this case the self-consistent charge densities differ only slightly from the simple Hückel charge densities. The final value of χ differs from the value given by the first iteration by an amount which corresponds to about 0·02 eV. In the large aromatic hydrocarbons the charge is

TABLE 3. EFFECT ON ω ON CHARGE DENSITIES OF SOME AROMATIC HYDROCARBON CATIONS

Position	q_r (Hückel)	q_r (first iteration)
Naphthalene		
1	0·819	0·869
2	0·931	0·907
9	1·000	0·949
Anthracene		
1	0·903	0·920
2	0·952	0·934
9	0·807	0·889
11	0·992	0·952
Phenanthrene		
1	0·884	0·930
2	0·998	0·946
3	0·901	0·922
4	0·946	0·926
9	0·828	0·880
11	0·973	0·936
12	0·970	0·960

[14] R. S. Mulliken, *Phys. Rev.* **74**, 736 (1948).

spread throughout most of the molecule, and the simple Hückel charge densities would not be expected to differ greatly from self-consistent charge densities. In Table 3 are listed the Hückel charge densities and the charge densities obtained from the first iteration for several aromatic hydrocarbons. The self-consistent charge densities will fall between the individual values. The changes involved are only a few hundredths of a unit at each position. Consequently we would not expect the value for χ which corresponds to the use of self-consistent charges to differ significantly from the values obtained in the first iteration in these cases.

The situation with cations of odd alternant hydrocarbons such as allyl and benzyl is rather different, however. In these cases the so called "starring process" can be carried out such that the number of starred positions is one more than the number of unstarred positions and no two starred positions are adjacent. In the Hückel approximation the positive charge density in these cations resides only on starred positions; these charge densities may be expected to differ substantially from the self-consistent charges. Table 4 lists the results for successive iterations of the allyl cation.

TABLE 4. SUCCESSIVE ITERATIONS FOR ALLYL CATION

No. of iterations	q_1	q_2	χ
0	0·500	1·000	
1	0·621	0·757	0·785
2	0·534	0·934	0·877
3	0·597	0·806	0·802
4	0·552	0·896	0·851
5	0·584	0·830	0·813
6	0·560	0·880	0·844
7	0·579	0·842	0·818
8	0·565	0·870	0·835
9	0·575	0·850	0·823
10	0·568	0·864	0·827
∞	0·571	0·858	0·825
equation (6)	0·624	0·753	0·787

The self-consistent charges fall about midway between the Hückel values and those given by the first iteration. The final value of χ differs from the value from the first iteration by an amount which corresponds to only 0·08 eV. The series of successive iterations for the benzyl cation, however, was not convergent. As shown in Table 5, the charge densities at different positions show increasing oscillation with progressive iteration. Starting with charge densities derived from a perturbation treatment (*vide infra*) which should be closer to self-consistent charges, successive iterations give oscillating charges with consequent variations in χ. This situation is probably associated with the form of molecular orbitals in aromatic rings. For comparison with related systems, our procedure was to start with Hückel charges and to use χ resulting from the first cycle of iteration.

Because of its symmetry, the case of benzene is unique. The degeneracy of the

highest orbitals leads to different cations, which probably cannot be made self-consistent by our procedure. Without further justification, we assumed an even distribution of positive charge on all six carbons and obtained χ from one cycle of iteration.

An alternative procedure for calculating the variation of the cation energy with ω involves the use of an approximation method. Coulson and Longuet-Higgins[15] have expanded the change in energy in a Taylor's series, the first two terms of which, equivalent to a second-order perturbation, are given in equation (5):

$$\delta E = \sum_r q_r \delta\alpha_r + \tfrac{1}{2} \sum_r \sum_s \pi_{rs} \delta\alpha_r \delta\alpha_s + \ldots \qquad (5)$$

They obtained simple expressions for the second derivatives, $\partial^2 E/\partial\alpha_r \partial\alpha_s$, identical to the atom–atom polarizabilities, π_{rs}, in terms of the energies and coefficients of the Hückel orbitals.

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TABLE 5. SUCCESSIVE ITERATIONS FOR BENZYL CATION

No. of iterations	q_1	q_2	q_3	q_4	q_7	χ
Starting with Hückel charges						
0	1·000	0·857	1·000	0·857	0·429	—
1	0·811	0·873	0·906	0·800	0·830	1·001
2	1·014	0·858	0·967	0·904	0·430	1·178
3	0·805	0·863	0·931	0·760	0·847	1·012
4	1·015	0·874	0·942	0·940	0·412	1·187
5	0·798	0·844	0·955	0·726	0·879	1·024
—	—	—	—	—	—	—
—	—	—	—	—	—	—
10	1·022	0·950	0·853	1·049	0·323	1·298
11	0·756	0·762	1·043	0·623	1·011	1·112
—	—	—	—	—	—	—
—	—	—	—	—	—	—
19	0·724	0·646	1·173	0·527	1·113	1·329
20	0·996	1·090	0·695	1·204	0·230	1·583
Starting with perturbation charges						
0	0·857	0·882	0·912	0·848	0·706	—
1	0·970	0·848	0·974	0·855	0·532	1·101
2	0·863	0·879	0·921	0·826	0·710	1·017
—	—	—	—	—	—	—
—	—	—	—	—	—	—
7	0·972	0·874	0·940	0·907	0·495	1·109
8	0·851	0·848	0·957	0·773	0·765	1·022

Equations (2) and (5) may be combined to yield equation (6):

$$\delta E = \chi \cong \omega \sum_r q_r(1 - q_r) + \frac{\omega^2}{2} \sum_r \sum_s \pi_{rs}(1 - q_r)(1 - q_s) \qquad (6)$$

This equation has been applied to a number of cations of odd alternant hydrocarbons.

[15] C. A. Coulson and H. C. Longuet-Higgins, *Proc. Roy. Soc.* A **191**, 39 (1947).

The values of χ derived in this way for allyl, benzyl and pentadienyl cations, 0·787, 0·972 and 1·020, respectively, are close to the values obtained by the rediagonalization process. The first and dominant term in equation (6) may be written in the form of equation (7), which shows its relationship to the "solvation energy parameter", Σq_r^2 recently derived by Mason[16] by a Born charging process:

$$\delta E \cong \omega(1 - \Sigma q_r^2) \tag{7}$$

The application of the Born charging concept to individual carbon atoms within a molecule is subject to a variety of criticisms. However, the resulting function was shown to correlate excellently with a number of carbonium ion reactivities in solution. The relationship of the resulting function to equation (7) demonstrates that Mason's results are equivalent to a first-order perturbation correction of the cation energy; the explicit value of ω in his treatment is absorbed in the slopes of the linear correlations. Inasmuch as the correction applies as well to cations in the gas phase in which solvation energies are obviously not involved, our interpretation of the Σq_r^2 function would appear to be more satisfactory than its interpretation as a "solvation energy parameter".

Muller and Mulliken[17] have applied a more elaborate molecular orbital theory with inclusion of overlap to the stabilization energies of several cations. Using the same type of variation of α with charge, they obtained best agreement with $\omega = 1{\cdot}4$ in precise agreement with our findings.

The slope of the correlation line, equation (4), corresponds to the value of β. This value, $-2{\cdot}11$ eV or $-48{\cdot}6$ kcal, is much larger than the value of about -20 kcal usually used for this parameter. The latter value is usually derived from empirical resonance energies of aromatic hydrocarbons and at most is suitable for use only for calculating similar resonance energies. Estimates of the vertical resonance energy of benzene of 65 to 80 kcal[18] correspond to values of β of $-1{\cdot}4$ to $-1{\cdot}7$ eV. Some other estimates of β are $-2{\cdot}2$ eV from the polarographic reduction of conjugated hydrocarbons,[19] $-2{\cdot}7$ eV from ultraviolet spectra,[19] and $-2{\cdot}3$ eV from phosphorescence spectra.[20] The value which we obtained fits in well with these determinations.

Models for hyperconjugation

Having established a standard correlation for unsaturated molecules, we examined several models for the hyperconjugation effect of a methyl group, using the relatively abundant data on electron-impact ionization potentials available for unsaturated hydrocarbons and radicals containing methyl groups. The first extensive theoretical treatment of hyperconjugation was that of Mulliken *et al.*,[21] who used a molecular orbital theory with inclusion of overlap. The hyperconjugative effect of the methyl group in this work was considered to operate through a p orbital on the methyl

[16] S. F. Mason, *J. Chem. Soc.* 808 (1958).
[17] N. Muller and R. S. Mulliken, *J. Amer. Chem. Soc.* **80**, 3489 (1958).
[18] D. F. Hornig, *J. Amer. Chem. Soc.* **72**, 5772 (1950); R. S. Mulliken and R. G. Parr, *J. Chem. Phys.* **19**, 1271 (1951); C. A. Coulson and S. C. Altmann, *Trans. Faraday Soc.* **48**, 293 (1952); G. Glockler, *Disc. Faraday Soc.* **10**, 26 (1951).
[19] G. J. Hoijtink and J. van Schooten, *Rec. Trav. Chim. Pays-Bas* **71**, 1089 (1952); *Ibid.* **72**, 691, 903 (1953).
[20] G. G. Hall, *Proc. Roy. Soc.* **A213**, 113 (1952).
[21] R. S. Mulliken, C. A. Riecke and W. G. Brown, *J. Amer. Chem. Soc.* **63**, 41 (1941).

carbon and a virtual p orbital formed by the three hydrogens operating as a pseudo-atom. In effect, the methyl group is treated in the simple theory as a vinyl group with modified α and β parameters (see Fig. 3).

$$C{-}C \equiv H_3 \equiv \underset{\alpha_1}{0} \overset{\beta_1}{\text{---}} \underset{\alpha_2}{0} \overset{\beta_2}{\text{---}} \underset{\alpha_3}{0}$$

FIG. 3. The methyl group as a modified vinyl group in the simple theory

The several subsequent treatments have differed mainly in the values assigned to these parameters and in the inclusion or neglect of overlap. The different parameters used are commonly given in terms of the standard α and β by use of equations such as (8) and (9). Values assigned by various authors to the different parameters associated with equations (8) and (9) and with Fig. 3 have been in the following ranges: h_1, 0 to $-0{\cdot}1$; h_2, 0 to $-0{\cdot}1$; h_3, 0 to $-0{\cdot}5$; k_1, 0·5 to 0·8; k_2, 2·0 to 4·8.[22]

$$\alpha_i = \alpha + h_i\beta \tag{8}$$

$$\beta_i = k_i\beta \tag{9}$$

Conjugation model (model C)

After reviewing the various values for the parameters used in the literature, we adopted the values $h_1 = 0$, $h_2 = -0{\cdot}1$, $h_3 = -0{\cdot}3$, $k_1 = 0{\cdot}8$ and $k_2 = 2{\cdot}8$. In setting up the energy matrices, methyl groups were treated as vinyl groups with these parameter values. The energies of each hydrocarbon or radical and the corresponding cation were carried through one cycle of iteration as described above. The χ values for

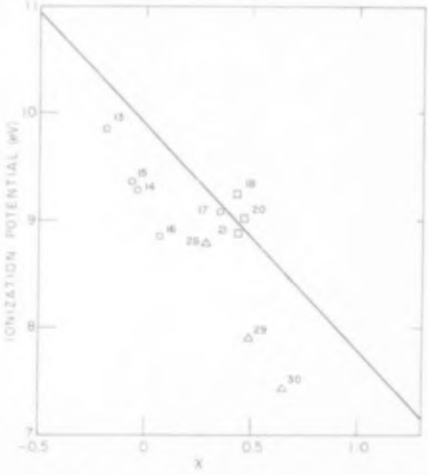

FIG. 4. Comparison of model C with the standard linear correlation. Numbers correspond to compounds in Table 6.

[22] J. S. Roberts and H. A. Skinner, *Trans. Faraday Soc.* **45**, 339 (1949); C. A. Coulson and V. A. Crawford, *J. Chem. Soc.* 2052 (1953); D. Peters, *Ibid.* 646 (1957); A. Loftus *J. Amer. Chem. Soc.* **79**, 24 (1957); N. Muller, L. W. Pickett and R. S. Mulliken, *Ibid.* **76**, 4770 (1954); Y. I'Haya *J. Chem. Phys.* **23**, 1165, 1171 (1955); Y. I'Haya, *Bull. Chem. Soc., Japan* **28**, 369, 376 (1955); H. H. Jaffe, *J. Chem. Phys.* **20**, 778 (1952); B. Pullman, M. Mayot and G. Berthier. *Ibid.* **18**, 257 (1950); A. Pullman and J. Metzger, *Bull. Soc. Chim. Fr.* **15**, 1021 (1948); G. Berthier and B. Pullman, *Trans. Faraday Soc.* **45**, 484 (1949); E. Heilbrenner and M. Simonetta, *Helv. Chim. Acta* **35**, 1049 (1952).

a number of methyl-substituted olefins, polyenes, aromatic hydrocarbons and radicals and the corresponding ionization potentials calculated from equation (4) are listed in Table 6, together with the experimental ionization potentials. The results are also plotted in Fig. 4. Comparison of the experimental points in Fig. 4 with the standard correlation line shows extremely poor agreement. Clearly the conjugation model, at least with the parameters assumed, is a poor one for the hyperconjugative effect of a methyl group. In general the model gives much less stabilization of a carbonium ion than does a methyl group.

Inductive model (model I)

Mackor *et al.*[23] have recently used an inductive model successfully for the effect of a methyl group on the basicities of aromatic hydrocarbons. In this model, any conjugation effect to a methyl group is ignored. Instead the methyl group by its inductive effect is considered to make the attached carbon somewhat more electropositive by the assignment of a small negative $\Delta\alpha$. Wheland and Pauling[24] have used a similar model in their original treatment of the orientation effect in aromatic substitution. Preliminary calculations suggested the use of $\delta\alpha = 0{\cdot}5\ \beta$. By using Lossing's values for the ionization potentials of *iso*propyl and *tert.*-butyl radicals (see Table 6), a damping effect

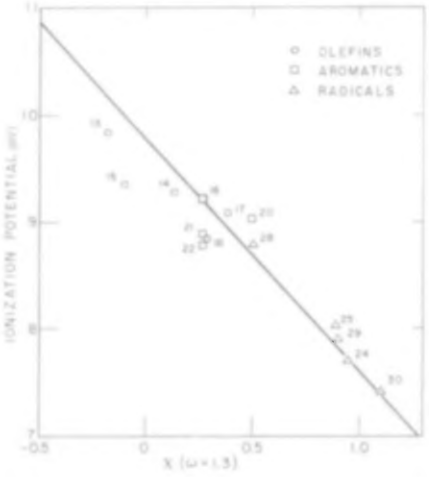

FIG. 5. Comparison of model *I* with correlation line for $\omega = 1{\cdot}3$. Numbers refer to compounds in Table 6.

of further methyl substitution on the same carbon is indicated. Hence, in the calculations, the results of which are listed in Table 6, the following values of $\delta\alpha$ were used for different extents of methyl substitution: $-0{\cdot}5\beta$ (one methyl group), $-0{\cdot}9\beta$ (two methyl groups), $-1{\cdot}1\beta$ (three methyl groups). If Stevenson's values for *iso*propyl and *tert.*-butyl radicals (see Table 6) are used, the damping factor disappears. These calculations were carried out before ω was established as 1·4. The $\delta\alpha$ values used were

[23] E. L. Mackor, G. Dallinga, J. H. Kruizinga and A. Hofstra, *Rec. Trav. Chim. Pays-Bas* **75**, 836 (1956); E. L. Mackor, A. Hofstra and J. H. Van der Waals, *Trans. Faraday Soc.* **54**, 186 (1958).
[24] G. W. Wheland and L. Pauling, *J. Amer. Chem. Soc.* **57**, 2086 (1935).

TABLE 6. COMPARISON OF CALCULATED AND EXPERIMENTAL IONIZATION POTENTIALS OF VARIOUS MODELS OF A METHYL GROUP

No.	Compound	$I_{expl.}$ (eV)	Model *C*		Model *I*		Model *I–C*	
			χ	$I_{calcd.}$ (eV)	χ ($\omega = 1{\cdot}3$)	$I_{calcd.}$ (eV) ($\omega = 1{\cdot}3$)	χ	$I_{calcd.}$ (eV)
13	Propylene	9·84[25]	−0·18	10·26	−0·23	10·28	−0·065	10·02
14	2-Butene (*trans*)	9·28[25]	−0·04	9·96	0·08	9·61	0·214	9·43
15	*iso*Butene	9·35[25]	−0·06	10·01	−0·15	10·11	0·103	9·66
16	Trimethyl-ethylene	8·85[25]	0·06	9·75	0·24	9·27	0·389	9·07
17	Isoprene	9·08[26]	0·35	9·14	0·32	9·09	0·397	9·04
18	Toluene	9·23[26]	0·43	8·97	0·26	9·21	0·302	9·24
20	*m*-Xylene	9·02[27]	0·46	8·91	0·42	8·88	0·392	9·05
21	*p*-Xylene	8·88[27]	0·44	8·95	0·21	9·33	0·321	9·20
22	Mesitylene	8·79[27]	—	—	0·18	9·39	—	—
24	α-Methylallyl	7·71[28]	—	—	0·85	7·95	0·871	8·04
25	β-Methylallyl	8·03[28]	—	—	0·83	7·99	0·870	8·04
26	*m*-Methyl-benzyl	7·65[29]	—	—	—	—	0·990	7·79
27	*p*-Methyl-benzyl	7·46[29]	—	—	—	—	1·033	7·74
28	Ethyl	8·78[30] 8·67[31]	0·28	9·29	0·50	8·71	0·572	8·67
29	*iso*Propyl	7·90[30] 7·43[32]	0·49	8·85	0·90	7·84	0·959	7·86
30	*tert.*-Butyl	7·42[33] 6·90[32]	0·64	8·53	1·10	7·40	1·253	7·24

determined as the best values for $\omega = 1{\cdot}3$. The calculated ionization potentials in Table 6 and the correlation line in Fig. 5 are those derived from a linear correlation with the standard points, with $\omega = 1{\cdot}3$. The $\delta\alpha$ values would probably require slight alterations for use with $\omega = 1{\cdot}4$. From the results listed in Table 6 and plotted in Fig. 5, it is apparent that the correlation is fair. Because of the simplicity of the model, this type of treatment would probably be satisfactory for many purposes. For the present purposes, however, we sought a model which would not only reproduce experimental ionization potentials to within a few tenths of an electron volt but would also reproduce trends within related families of molecules. Model *I* shows serious deficiencies in reproducing patterns with related compounds; for example, the difference between

[25] R. E. Honig, *J. Chem. Phys.* **16**, 105 (1948).
[26] J. D. Morrison and A. J. C. Nicholson, *J. Chem. Phys.* **20**, 1021 (1952).
[27] F. H. Field and J. C. Franklin, *J. Chem. Phys.* **22**, 1895 (1954).
[28] C. A. McDowell, F. P. Lossing, I. H. S. Henderson and J. B. Farmer, *Canad. J. Chem.* **34**, 345 (1956).
[29] J. B. Farmer, F. P. Lossing, O. G. H. Marsden and C. A. McDowell, *J. Chem. Phys.* **24**, 52 (1956).
[30] J. B. Farmer and F. P. Lossing, *Canad. J. Chem.* **33**, 861 (1955).
[31] J. A. Hipple and D. P. Stevenson, *Phys. Rev.* **63**, 121 (1943).
[32] D. P. Stevenson, personal communication; see *Disc. Faraday Soc.* **10**, 35 (1951).
[33] F. P. Lossing, personal communication.

2-butene and *iso*butene is exaggerated; there is almost no calculated difference between α- and β-methylallyl radicals (*vide infra*). This situation would not be expected to change significantly for appropriate calculations with $\omega = 1{\cdot}4$. Nevertheless, model *I* showed much better over-all agreement than did model *C*.

Inductive–conjugation model (*model I–C*)

The encouraging results with the inductive model suggested its combination with the conjugation model. The methyl group is again treated as a modified vinyl group but the attached carbon is made effectively electropositive by the assignment of a negative $\delta\alpha$. Based on some preliminary calculations, we adopted the following values of h and k relating to the α and β quantities in Fig. 3: h_1, $-0{\cdot}3$; h_2, $-0{\cdot}3$; h_3, $-0{\cdot}6$;

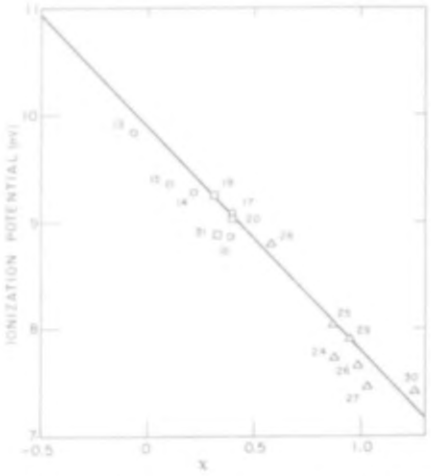

FIG. 6. Comparison of model *I–C* with experimental ionization potentials, with $\omega = 1{\cdot}4$. Numbers correspond to compounds in Table 6.

k_1, 0·8; k_2, 2·8. The values of α assigned to the carbon and hydrogen of the methyl group are such as to make these atoms at least as electropositive as the attached carbon. For compounds containing two or three methyl groups on a single carcorresponding values used for h_1 are $-0{\cdot}6$ and $-0{\cdot}9$, respectively; i.e., no damping factor was used. The results of the calculations carried through one iteration are listed in Table 6 and are plotted in Fig. 6. In Fig. 6, the Lossing values for *iso*propyl and *tert.*-butyl radicals were used. On the whole, this model is fairly successful. The average deviation between experimental and calculated ionization potentials is less than 0·2 eV. On closer examination, however, we find important limitations in tracing the patterns within families of compounds. For example, α-methylallyl radical and β-methylallyl radical calculate to have the same ionization potential. We would expect a conjugated methyl group to stabilize allyl cation more than a cross-conjugated methyl group; experimentally, these radicals differ in ionization potential by 0·3 eV. Similarly, the methyl group in *p*-methylbenzyl radical calculates to provide substantially less stabilization of the cation than is experimentally observed. Consequently,

TABLE 7. CALCULATIONS FOR MODEL *H*

No.	Compound	$I_{expt.}$ (eV)	*M* hydrocarbon	*M* cation	χ	$I_{calcd.}$ (eV)	Hyperconjugation per methyl	
							Hydrocarbon	Cation
13	Propylene	9·84[24]	8·889	8·870	−0·019	9·92	0·149β	0·500β
14	2-Butene (*trans*)	9·28[24]	15·624	15·930	0·306	9·23	0·142	0·480
15	*iso*Butene	9·35[24]	15·644	15·890	0·246	9·36	0·152	0·460
16	Trimethylethylene	8·85[24]	22·363	22·914	0·551	8·72	0·141	0·448
17	Isoprene	9·08[25]	11·392	11·839	0·447	8·94	0·141	0·279
18	Toluene	9·23[25]	14·741	15·157	0·416	9·00	0·141	0·390
19	*o*-Xylene	8·97[27]	21·480	22·033	0·553	8·71	0·140	0·333
20	*m*-Xylene	9·02[26]	21·484	22·031	0·547	8·73	0·142	0·332
21	*p*-Xylene	8·88[26]	21·480	21·987	0·507	8·81	0·140	0·310
23	1, 2, 3-Trimethylbenzene	8·75[27]	28·217	28·909	0·692	8·42	0·139	0·314
24	α-Methylallyl	7·71[27]	9·595	10·627	1·032	7·70	0·167	0·414
25	β-Methylallyl	8·03[27]	9·566	10·453	0·887	8·01	0·138	0·240
26	*m*-Methylbenzyl	7·65[28]	15·462	16·529	1·067	7·64	0·167	0·414
27	*p*-Methylbenzyl	7·46[28]	15·467	16·579	1·112	7·53	0·138	0·240
28	Ethyl	8·78[29] 8·67[30]	6·784 —	7·410 —	0·626 —	8·56 —	0·184 —	0·810 —
29	*iso*Propyl	7·90[29] 7·43[31]	13·552 —	14·634 —	1·082 —	7·60 —	0·176 —	0·717 —
30	*tert.*-Butyl	7·42[32] 6·90[31]	20·307 —	21·750 —	1·443 —	6·83 —	0·169 —	0·650 —

this model is of limited usefulness. This situation is not improved by any reasonable changes in the values used for the parameters. At least in the simple theory with neglect of overlap, the vinyl model is a poor representation of a methyl group.

Heteroatom model (model H)

Matsen[34] and Stevenson[35] have used a model in which the methyl group is treated as a single heteroatom, *X*, which contributes a pair of electrons to the π system. In applying this model we used $\beta_{C-X} = 0{\cdot}8\beta$ and tried various values of α_X. Best results were obtained with $h_X = 3{\cdot}3$. The α of the attached carbon was not altered. The results of the calculations with this model, carried through one cycle of iteration, are listed in Table 7 and are plotted in Fig. 7. Table 7 also records the total bonding energies in the form of *M* values for each hydrocarbon or radical and the corresponding

[34] F. A. Matsen, *J. Amer. Chem. Soc.* **72**, 5243 (1950).
[35] D. P. Stevenson, personal communication; also see F. H. Field and J. L. Franklin, *Electron Impact Phenomena* p. 124. Academic Press, New York (1957).

cation. Each total energy is of the form of equation (10) in which n is the number of π electrons and $M\beta$ is the total π-bonding energy:

$$E = n\alpha + M\beta \tag{10}$$

The agreement, on the whole, is quite good. The aliphatic olefins fit well. The trend in the aromatic hydrocarbons is reproduced except for *p*-xylene. It is interesting that all four models used give a higher calculated ionization potential for *p*-xylene than for *m*-xylene and suggest that the experimental values may be slightly in error. The aromatic hydrocarbons in absolute value, however, are significantly displaced from the correlation line (*vide infra*). The effect of a methyl group attached to allyl radical or to benzyl radical is excellently accounted for in this model. The average deviation between experimental and calculated ionization potentials for these three sets of compounds is only 0·11 eV. The situation with the simple alkyl radicals is difficult to

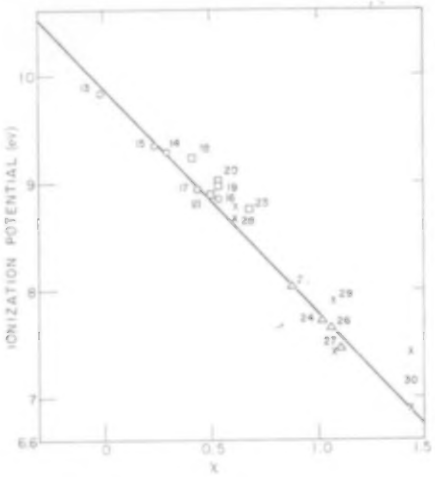

FIG. 7. Comparison of model *H* with experiment. Numbers correspond to compounds in Table 7.

evaluate. The calculated result for ethyl radical agrees fairly well with both Stevenson's and Lossing's experimental values. The values given by these authors differ by 0·5 eV for *iso*propyl radicals and for *tert.*-butyl radicals (see Table 7). The points for the three alkyl radicals are shown by pairs of crosses in Fig. 7. All we can say at this time is that the calculated results are apparently reasonably close to the actual values. The calculated ionization potentials for these simple radicals are very dependent on the parameter values used. The observed trends suggest that $\beta_{C-X} = 0{\cdot}7\beta$ may be a better assumption. For this value of β_{C-X}, preliminary results indicate that the associated α_X has a h_X value of about 3.0.

It should be noted that in the model used the methyl group heteroatom was considered to have no inductive effect on the attached carbon; α for the attached carbon was not changed and no "auxiliary inductive parameter"[36] was used. When attempts were made to include such an inductive effect by assigning a small negative h to the

[36] R. D. Brown, *Quart. Rev.* **6**, 63 (1952).

TABLE 8. SUCCESSIVE ITERATIONS OF PROPYLENE CATION (MODEL H)

No. of iterations	q_1	q_2	q_3	χ
0	1·918	0·536	0·547	—
1	1·884	0·561	0·555	−0·019
2	1·890	0·551	0·559	0·044
3	1·889	0·557	0·554	0·033
4	1·889	0·553	0·558	0·035
5	1·889	0·556	0·556	0·035
6	1·889	0·554	0·557	0·035
∞	1·889	0·554	0·556	0·035

TABLE 9. SUCCESSIVE ITERATIONS OF ETHYL CATION (MODEL H, $h_x = 3{\cdot}5$)

No. of iterations	q_1	q_2	χ
0	1·909	0·091	—
1	1·827	0·173	0·572
2	1·850	0·150	0·765
3	1·844	0·156	0·710
4	1·846	0·154	0·725
5	1·845	0·155	0·721
6	1·845	0·155	0·722
7	1·845	0·155	0·722

attached carbon, it was found impossible to get reasonable agreement with the correlation curve.

In several systems we examined the effect of further iteration to determine whether this model would converge generally to a self-consistent energy and pattern of charge densities and to see if the self-consistent value differed importantly from the first iterated values. Propylene cation (Table 8) and ethyl cation (Table 9) converged rapidly. The self-consistent value of χ for propylene differs from first iterated value by an amount which corresponds to 0·1 eV and agrees better with the experimental value. The calculations in the ethyl case were made using a value of h for the methyl group heteroatom, X, of 3·5. The final χ value differed from the first iterated value by an amount which corresponds to a reduction in the ionization potential of 0·3 eV. A similar result would be expected for $h = 3{\cdot}3$. This result further suggests the use of a smaller β_{C-X}. Toluene (Table 10) was found to be unstable to successive iterations. The charge densities as in the benzyl case oscillated and gave progressive divergence. The charge densities of the first and second iterations were averaged and were used to initiate a new series of iterations. The use of these charges (SCF charges) gave a first iteration χ corresponding to a calculated ionization potential of 9·17 eV, in good agreement with experiment. However, the system was still unstable and showed the

same type of progressive divergence noted above, probably for the same reasons as the instability of benzyl.

Hyperconjugation energies tabulated in Table 7 were derived for each of the hydrocarbons or radicals and the corresponding cations by subtracting from the total energy the energy of the parent unsubstituted compound and the energies of the attached

TABLE 10. SUCCESSIVE ITERATIONS OF TOLUENE CATION (MODEL *H*)

No. of iterations	q_7	q_1	q_2	q_3	q_4	x
Starting with Hückel charges						
0	1·935	0·654	0·920	0·933	0·705	—
1	1·969	1·073	0·726	0·700	1·107	0·416
2	1·934	0·564	0·964	1·002	0·569	0·552
3	1·970	1·120	0·704	0·653	1·197	0·555
4	1·936	0·548	0·965	1·030	0·526	0·636
5	1·970	1·123	0·706	0·634	1·228	0·597
—	—	—	—	—	—	—
—	—	—	—	—	—	—
10	1·936	0·556	0·942	1·062	0·500	0·675
11	1·969	1·105	0·723	0·612	1·256	0·620
Starting with SCF charges						
0	1·952	0·819	0·845	0·851	0·838	—
1	1·928	0·667	0·920	0·929	0·708	0·334
2	1·696	1·067	0·727	0·702	1·105	0·420
3	1·934	0·567	0·963	1·001	0·570	0·547
4	1·970	1·118	0·704	0·654	1·196	0·553
5	1·936	0·549	0·965	1·030	0·526	0·635

methyl groups. The hyperconjugation energies per methyl group for the hydrocarbons and radicals are relatively constant at 0·14–0·18β (7–9 kcal/mole). These relatively large energy values will become substantially reduced when the effects of bond contraction and electron correlation are considered. The hyperconjugation energies for the cations are much larger and more variable. The results agree with the common organic chemical view that a methyl group stabilizes a carbonium ion much more than a neutral hydrocarbon or radical. The observed variations also agree with qualitative organic thought; the methyl group in ethyl cation does much better at stabilizing a positive charge than does the methyl group in crotyl cation which in turn is better than the methyl group in *p*-methylbenzyl cation.

Because of the simplicity of the simple molecular orbital theory and its many theoretical deficiencies the success or failure of a model in the simple theory cannot strictly be used as evidence for or against specific effects embodied in the model. The success of model *H*, however, does *suggest* that appropriately oriented sigma electrons in an alkyl group are available for π conjugation; i.e., that substantial stabilization of carbonium ions by hyperconjugation does occur. There is no reason in principle why other alkyl groups could not also be treated by the same model, albeit, perhaps with

slightly altered values of β_{C-X} and α_X. There are not enough ionization potential data, however, for meaningful comparisons using the present technique.

Other systems

The techniques described in this paper were applied to the calculation of the ionization potentials of several compounds which have not been experimentally determined. These values are listed in Table 11. It is interesting that the β-phenylallyl radical calculates to have an ionization potential similar to that of the allyl radical itself; cinnamyl radical, in which the phenyl group is now directly conjugated, calculates to have a lower ionization potential. This effect of conjugation versus non-conjugation is also seen to a lesser extent in 1- and 2-phenylbutadiene.

TABLE 11. IONIZATION POTENTIALS OF SOME UNMEASURED COMPOUNDS

Compound	χ	I (eV)
1-Methylbutadiene	0·510	8·80
Cinnamyl radical	1·094	7·57
β-Phenylallyl radical	0·798	8·20
Stilbene	0·687	8·43
1-Phenylbutadiene	0·648	8·52
2-Phenylbutadiene	0·545	8·73
Azulene	0·748	8·30
Pyrene	0·826	8·13

Calculations

Most of the calculations were performed with an IBM 701 digital computer. The secular matrix was input as the half-matrix. The off-diagonal elements, which are non-zero only when a bond exists between the corresponding atoms, were used to set up a list of the bonds which was later printed as a "bond-key" and served as a check that the input matrix actually corresponded to the desired compound. The matrix diagonalization program which utilized the Jacobi method was written by Mr. John Newhaus. The eigenvectors and eigenvalues were used to compute the required charge densities, bond orders and atom–atom polarizabilities by the usual equations.[15] Different programs were written for the calculations using equation (6), the repeated successive iterations of various compounds and calculations with various values of ω. The last program gave single iteration results with the ω values of 0·5, 0·75, 1·0 and 1·5. Unfortunately, because of an error in the program, the calculations for each value of ω after the first were made not on the Hückel charge densities but on the charge densities resulting from the previous ω. Hence the interpolated values for $\omega = 1{\cdot}4$ for a number of cases in model *I* and model *I–C* correspond in effect to more than one cycle of iteration. The results for these compounds differ from the true first iterated values by an amount which corresponds to only a few hundredths of an electron volt in the ionization potential. In the programs used with the heteroatom model the appropriate changes were incorporated to account for the contribution of two electrons by each "heteroatom".

Acknowledgement—We thank Dr. D. P. Stevenson for several valuable discussions and for information in advance of publication.

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A RE-EVALUATION OF CONJUGATION AND HYPER-CONJUGATION: THE EFFECTS OF CHANGES IN HYBRIDISATION ON CARBON BONDS

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THIS paper falls into three sections.

In the first, we examine the currently accepted evidence for the delocalisation of bonds in polyenes, olefines, etc., and show it to be inconclusive.

In the second, we give three independent estimates of the length of a pure single σ bond between sp^2 carbon atoms which indicate that it is close to the value for the central bond in butadiene. We also estimate the bond energies of bonds formed by sp^2 carbon atoms, and find that the apparent "resonance energy" of butadiene can be ascribed quantitatively to the variation in bond energy with hybridisation.

In the third section we consider the status of conjugation in general terms; we shall conclude that the naive resonance picture is correct, in that resonance is important only in molecules for which more than one classical (unexcited) structure can be written.

The evidence for bond delocalisation

Five lines of evidence are commonly quoted as evidence for the delocalisation of bonds in conjugated and hyperconjugated systems*:

(*a*) The shortening of σ bonds in such systems; for example, the single C–C bonds in butadiene and methylacetylene are approximately 1·46 Å in length, much less than the value (1·54 Å) found in saturated hydrocarbons or diamond.

(*b*) The fact that the heats of formation of such molecules are greater than the sum of their bond energies; and the heats of hydrogenation per double bond are less than the heat of hydrogenation of ethylene.

(*c*) The fact that hyperconjugated hydrocarbons such as toluene are polar.

(*d*) The fact that conjugated and hyperconjugated molecules show a light absorption very different from that of unconjugated analogues.

(*e*) The fact that conjugated and hyperconjugated molecules differ in chemical reactivity from unconjugated analogues.

Criticism of the evidence for delocalisation

(*a*) It has long been recognised[1, 2] that bonds formed by sp^2 carbon atoms must

* The terms conjugation and hyperconjugation are used here as designations of structural features, with no reference to their theoretical interpretation.

[1] R. S. Mulliken, C. A. Rieke and W. G. Brown, *J. Amer. Chem. Soc.* **63**, 41 (1941).
[2] C. A. Coulson, *Victor Henri Memorial Volume; Contribution à l'Étude de la Structure Moléculaire* p. 15. Desoer, Liège (1948); *Proc. Roy. Soc.* A **207**, 91 (1951).

be shorter than analogous bonds formed by sp^3 carbon. Unless the degree of shortening can be estimated, no conclusions can be drawn from the lengths of single bonds in molecules such as butadiene or methylacetylene. Mulliken *et al.*[1] and Coulson[2] estimated the length (r_1) of the pure sp^2–sp^2 C–C bond by assuming additivity of covalent radii, and estimating the covalent radius of sp^2 carbon by comparison of the CH bond lengths in methane or ethane (1·095 Å) with that in ethylene (1·07 Å). This leads* to a predicted value of about 1·50 Å for r_1. This argument is certainly not conclusive; for there is no theoretical justification for the rule of additivity of covalent radii, and it tends in any case to fail for hydrides.

(*b*) Likewise the bond energies of bonds formed by sp^2 carbon must be greater than those of analogous bonds formed by sp^3 carbon. This obviously invalidates any calculations of "resonance energies" by comparison of observed heats of formation with those calculated from current tables of bond energies; for the latter are based on the assumption that bond energies are unaffected by changes in hybridisation. Thus the C=C bond energy is deduced from the heat of formation of ethylene by assuming that the bond energies of the CH bonds are the same as in a paraffin; this cannot be the case.

The same applies to the calculation of resonance energies from heats of hydrogenation. Consider the following thermochemical argument, x being the heat of hydrogenation of ethylene, E_{RS} the bond energy of a single bond between atoms R, S involving sp^3 carbon atoms and E'_{RS} the corresponding value for sp^2 carbon atoms:

$$2\,CH_2{=}CH_2 + 2H_2 \rightarrow 2\,C_2H_6 + 2\,x$$
$$2\,CH_2{=}CH_2 \rightarrow CH_2{=}CH{-}CH{=}CH_2 + H_2 + E'_{CC} + E_{HH} - 2E'_{CH}$$
$$2\,CH_3{-}CH_3 \rightarrow C_4H_{10} + H_2 + E_{CC} + E_{HH} - 2E_{CH}$$

hence

$$CH_2{=}CH{-}CH{=}CH_2 + 2\,H_2 \rightarrow C_4H_{10} + 2\,x - [(E'_{CC} - E_{CC}) - 2(E'_{CH} - E_{CH})] \qquad (1)$$

The "resonance energy" of butadiene is defined† as the difference between the heat of hydrogenation of butadiene and that of two molecules of ethylene. Clearly this will include a term E_h, given by:

$$E_h = (E'_{CC} - E_{CC}) - 2(E'_{CH} - E_{CH}) \qquad (2)$$

which represents the effect of the different hybridisation of the carbon atoms in the unsaturated and saturated hydrocarbons. Obviously E_h has nothing to do with delocalisation of electrons or resonance; and unless we can estimate E_h and show it to be less than the observed "resonance energy", we cannot tell from heats of hydrogenation whether resonance is, or is not, important in butadiene.

Exactly the same situation arises in the case of hyperconjugation, as is shown by the following argument for propene:

* Recent estimates[3, 4] of the CH bond length in ethylene (1·085 Å) lead to a value of 1·52 Å for r_1.

† The use of this naive definition, in the place of comparisons with "reference compounds" (here butene-1), will be justified later.

[3] L. S. Bartell and R. A. Bonham, *J. Chem. Phys.* **27**, 1414 (1957).
[4] O. Bastiansen, Lisa Hedberg and K. Hedberg, *J. Chem. Phys.* **27**, 1311 (1957).

$$CH_2{=}CH_2 + H_2 \rightarrow C_2H_6 + x$$
$$CH_2{=}CH_2 + CH_4 \rightarrow CH_2{=}CH \cdot CH_3 + H_2 + E''_{CC} + E_{HH} - E_{CH} - E'_{CH}$$
$$C_2H_6 + CH_4 \rightarrow C_3H_8 + H_2 + E_{CC} + E_{HH} - 2E_{CH} \quad (3)$$

where E''_{CC} is the bond energy for a σ bond between an sp^2 carbon and an sp^3 carbon.

Hence:

$$CH_2{=}CH{-}CH_3 + H_2 \rightarrow C_3H_8 + x - [(E''_{CC} - E_{CC}) - (E'_{CH} - E_{CH})] \quad (4)$$

Therefore the apparent "resonance energy" of propene will contain a term E'_h, given by

$$E'_h = (E''_{CC} - E_{CC}) - (E'_{CH} - E_{CH}) \quad (5)$$

The same situation will arise quite generally. The experimental resonance energy will contain a contribution due to changes in hybridisation given by:

$$(E_h)_{total} = mE_h + nE'_h \quad (6)$$

where m is the number of single bonds between pairs of sp^2 carbon atoms, and n that of bonds between sp^2 and sp^3 carbon atoms in a classical structure for the hydrocarbon.

Obviously, similar arguments will apply to compounds containing heteroatoms: for example to $\alpha\beta$-unsaturated ketones.

(*c*) As Walsh[5] has emphasised, sp^2 carbon must be more electronegative than sp^3 carbon. Therefore bonds between sp^2 and sp^3 carbon atoms must be polar, for example:

$$\underset{sp^3}{CH_3} \rightarrow \underset{sp^2}{CH}{=}CH_2 \qquad \underset{sp^3}{CH_3} \rightarrow \underset{sp^2}{C_6H_5}$$

Unless the magnitude of this dipole can be estimated and shown to be less than the observed moment of propene or toluene, one cannot conclude from the polarity of those hydrocarbons that the bonds to methyl are not single.

(*d*) The light absorption of a compound is determined by the *difference* in energy between two different states, the ground state and an excited state. One cannot therefore conclude from the light absorption of a conjugated molecule that the ground state is non-classical; the differences from analogous unconjugated molecules may lie entirely in the excited states. One would certainly expect a much greater degree of electron delocalisation in the excited state than in the ground state, where all the electrons are paired; so this argument is by no means merely a piece of provocative sophistry.

(*e*) Exactly the same argument applies to chemical reactivity, which again is determined by the difference in energy (strictly free energy) between *two* different states, the initial state and the transition state. Here again one would expect the transition state for the reaction of a molecule such as butadiene to be more delocalised than the parent hydrocarbon; for the products of such reactions (e.g., addition of ions or radicals) are either allyl derivatives of π-complexes, in which the electrons must be more highly delocalised than they are in butadiene.

The arguments for delocalisation or resonance in simple conjugated systems, or in hyperconjugated systems, are therefore inconclusive. Obviously there *are* systems in

[5] A. D. Walsh, *Trans. Faraday Soc.* **43**, 60 (1947).

which delocalisation must be important; for example, benzene or graphite, where all the bonds have the same length. But the extrapolation to systems such as butadiene or propylene has no justification. We have also seen that most of the current interpretation of the thermochemistry of carbon compounds needs complete revision.

Preliminary estimate of the length of the $C(sp^2)$–$C(sp^2)$ *bond*

Accurate measurements of bond lengths in a variety of compounds containing triply bound carbon have shown[6] that the lengths of adjacent C–C single bonds are constant to within two or three thousandths of an angström, having the values shown in Table 1.

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TABLE 1. EQUILIBRIUM LENGTHS OF VARIOUS CC BONDS

Bond	Equilibrium length (Å)
	1·542 ± 0·001
	1·460 ± 0·003
	1·380 ± 0·002
$H_2C{=}CH_2$	1·353
$H_2C{=}C{=}CH_2$	1·309

The same value for the "hyperconjugated" C–C single bond is observed not only in a range of methylacetylenes, but also in acetonitrile and trifluoroacetonitrile; and the value for the "conjugated" single bond is likewise the same in cyanoacetylene or cyanogen as in polyacetylenes. The constancy of these bond lengths in compounds of very different types, and the fact that the contraction (0·082 Å) in passing from an sp^3–sp^3 bond to an sp^3–sp one is, within the limits of experimental error, the same as that (0·080 Å) in passing from an sp^3–sp bond to an sp–sp one, suggest very strongly indeed that the contractions are due to a change in covalent radius of carbon with hybridisation and not to any resonance or delocalisation effect.

If one assumes that the covalent radius of carbon is a linear function of its *s*-character, one finds for the covalent radius of sp^2 carbon (33 per cent *s*) the value 0·745 Å, corresponding to a value of r_1, the $C(sp^2)$–$C(sp^2)$ bond length, of 1·49 Å. This argument suggests that the values assumed for r by previous workers are too great.

Table 1 also gives values[6] for the bond lengths in ethylene and allene. Here no resonance effects are possible and the contraction in allene must be due to the different hybridisation (sp) of the central carbon atom. If we assume that the change in hybridisation affects the lengths of single and double bonds equally, we then find for the various covalent radii of carbon:

[6] See L. F. Herzberg and B. P. Stoicheff, *Nature, Lond.* **175**, 79 (1955).

$$(sp^3)\text{–}(sp) = 0{\cdot}08 \text{ Å} : (sp^2)\text{–}(sp) = 0{\cdot}044 \text{ Å} \tag{7}$$

whence:

$$(sp^3)\text{–}(sp^2) = 0{\cdot}036 \text{ Å} \tag{8}$$

and so:

$$r_1 = 1{\cdot}543 - 2(0{\cdot}036) = 1{\cdot}471 \text{ Å} \tag{9}$$

This argument is uncertain at two points. First, the length of the C=C bond in ethylene is uncertain, a recent study[3] by electron diffraction having given the value 1·334 Å. This value implies $r_1 = 1{\cdot}43$ Å, which seems too small. Secondly, the assumption that changes in covalent radius affects both C–C and C=C bond length equally is suspect, though one can show that the differences should not be large.

Inclusion of σ bond compression energy in MO *calculations*

A second estimate of r_1 was obtained in the course of a different investigation, one which led us to consider in detail the properties of bonds involving sp^2 carbon atoms.

Various attempts[7] have been made to include σ-bond compression in MO calculations; most of these have either used unrealistic (parabolic) potential functions, or have depended on symmetry properties of special molecules (e.g., benzene). No general method has been published for including in MO calculations the effects of σ-bond compression, using an arbitrary potential function. The following considerations provide such a method.

Making the usual assumption that σ and π electrons can be treated independently, we can write the total energy (E) of a conjugated molecule in the form:

$$E = E_\pi + E_c \tag{10}$$

where E_π is the total energy of the π electrons and E_c is the energy required to compress the σ bonds to the lengths they have in the actual molecule. We may write:

$$E_c = \sum_{r<s} \sum C_{rs} \tag{11}$$

where C_{rs} is the compression energy of the σ bond between the (adjacent) atoms r, s. Now in the simple Hückel treatment, with or without inclusion of overlap,

$$E_\pi = \sum_r q_r \alpha_r + 2 \sum_{r<s} \sum p_{rs}\beta_{rs} \tag{12}$$

where q_i, p_i are the π-electron charge density at, and Coulomb integral of, atom i; and p_{ij}, β_{ij} are the bond order and resonance integral of the bond between atoms i and j. Combining equations (10) and (12):

$$E = \sum_r q_r \alpha_r + 2 \sum_{r<} \sum p_{rs}\beta_{rs} + \sum_{r<s} \sum c'_{rs}$$

$$= \sum_r q_r \alpha_r + 2 \sum_{r<s} \sum p_{rs}\beta'_{rs}$$

where:

$$\beta'_{rs} = \beta_{rs} + \frac{c_{rs}}{2p_{rs}} \tag{14}$$

[7] E. S. Lennard-Jones, *Proc. Roy. Soc.* A **158**, 280 (1937); H. C. Longuet-Higgins and F. H. Burkitt, *Trans. Faraday Soc.* **48**, 1077 (1952).

Since β, c and p are all one-valued functions of bond length, so also is β'. Moreover equations (12) and (13) are identical in form. It follows that if we carry out a Hückel treatment, replacing β by β', and making the treatment self-consistent for the variation in β' with bond length, we obtain a value for E instead of E_π; and the corresponding values of the bond lengths are those which minimise E, the *total* energy of the molecule. This treatment therefore allows explicitly for the effect of σ-bond compression. To complete the calculation, we need to know β as a function of bond length. This can be done as follows. Consider the conversion of a pure C–C single bond of length r_1 to a double bond of length r. This can be done in stages (Fig. 1). The bond is first

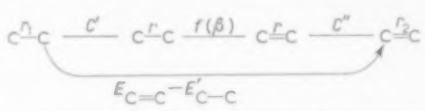

FIG. 1. Estimation of β as a function of bond length.

compressed to length r, with an increase in energy C', equal to the compression energy of the single bond; and then the π-component is introduced, with a change in energy calculated by MO theory as some function $f(\beta)$ of β.

Now the energy change can also be estimated in another way. First we convert the C–C single bond of length r_1 to a C=C double bond of equilibrium length r_2, the energy difference being equal to the difference between the C=C bond energy ($E_{C=C}$) and that (E'_{CC}) for a single bond between sp^2 carbon atoms. Next we stretch the double bond to length r, with a change in energy C''. Equating these two estimates:

$$C' + f(\beta) = E_{C=C} - E'_{CC} + C'' \tag{15}$$

whence

$$f(\beta) = E_{C=C} - E'_{CC} + C'' - C' \tag{16}$$

In this equation $E_{C=C}$ is known, and C'' can be found from any suitable potential function. In order to estimate β, we also need to know E'_{CC} and C'. It is natural to assume Morse functions for calculating compression energies; if so, the function for C' will involve r_1 and E'_{CC}, and that for C'', r_2 and $E_{C=C}$. This shows why we became interested in estimating r_1 and E'_{CC}.

Note that, although the above argument has been based on the simple Hückel form of the MO method, exactly the same treatment can be used in the SCF approach; for the one-electron terms in the Roothaan equations are identical in form with the Hückel expressions, and so if the one-electron resonance integrals β are replaced by the modified quantities β' [equation (14)] the SCF treatment will automatically lead to results corrected for σ-bond compression. Since solution of the Roothaan equations involves in any case an iterative procedure, no extra labour would be involved in this refinement.

In our preliminary work on bond lengths we have used the Hückel treatment, but we plan to carry out similar calculations by the SCF method.

A second estimate of r_1, and estimates of E'_{CC}

The treatment outlined in the previous section can be used to estimate bond lengths in conjugated systems in terms of the quantities r_1 and E'_{CC}. We were thus able to

calculate* the bond lengths in benzene and graphite in terms of these quantities; the resulting expressions could be treated as a pair of simultaneous equations for r_1 and E'_{CC}, and we were able to solve these with the aid of a digital computer. The results were:

$$r_1 = 1{\cdot}479 \text{ Å}; \quad E'_{CC} = 100 \text{ kcal/mole} \tag{17}$$

The agreement of r_1 with previous estimates, and with the experimental value for the length of the central bond in butadiene, is remarkable, and certainly supports the idea that the length of that bond is not due to any significant resonance effects in butadiene; for the calculation treated r_1 and E'_{CC} as a pair of parameters whose values were in no way prejudged.

The values given in equation (13) were checked in three independent ways. First, the calculations also led to values for the total heats of formation of benzene and graphite, and these agreed well with experiment. Secondly, the values for r_1 and E'_{CC} fitted well an empirical relation between bond energy and bond length, the derivation of which is described below. Thirdly, the resulting bond energies led [cf. equation (1)] to a predicted heat of hydrogenation of butadiene in good agreement with experiment; this point, which is discussed in detail later in this paper, shows that both the central bond length and the heat of hydrogenation of butadiene can be consistently interpreted with a non-resonating model.

Empirical relations between bond energy and bond length

Glockler[8] and others have shown that the heats of formation of carbon compounds can be consistently interpreted on the assumption that bond energy is a one-valued function of bond length. We preferred, however, to derive new relations of this kind for CC and CH bonds, since we felt that the published ones were open to criticism.

We adopted three-parameter relations of the form:

$$E = a_1 r_1^{-1} + a_2 r_2^{-2} + a_3 r_3^{-3} \tag{18}$$

for both carbon–carbon and carbon–hydrogen bonds. The six parameters were evaluated by assuming the heats of formation (with $L_c = 170$ kcal/mole) and bond lengths for diamond, methane, ethane, ethylene, benzene and acetylene, the spectroscopic bond lengths being corrected for residual energy to make them compatible with thermochemical data. The relations so obtained for the bond energies (in kcal/mole) at 25° were:

$$(E_{CC})_r = -\frac{1140{\cdot}593}{r} + \frac{3252{\cdot}755}{r^2} - \frac{1991{\cdot}129}{r^3} \tag{19}$$

$$(E_{CH})_r = \frac{1125{\cdot}03}{r} - \frac{2477{\cdot}006}{r^2} + \frac{1376{\cdot}444}{r^3} \tag{20}$$

As a check, the heat of atomisation of graphite was calculated, the value (171 kcal/mole) being in satisfactory agreement with experiment. The values for r_1 and E'_{CC} in equation (17) fit equation (19).

* These calculations were carried out by the simple MO treatment, with inclusion of overlap: the overlap integrals were those calculated for SCF AO's.

[8] G. Glockler, *J. Chem. Phys.* **21**, 1242, 1249 (1953); *J. Phys. Chem.* **61**, 31 (1957).

The corresponding values of bond lengths and bond energies for the various CC and CH bonds are listed in Table 2; here E_e and r_e are the equilibrium values for the bond energy and bond length, and E_0 and r_0 are the values appropriate to thermochemical calculations at 25°C.

TABLE 2. BOND ENERGIES AND BOND LENGTHS FOR CARBON BONDS

Bond	Bond lengths (Å)		Bond energies (kcal/mole)	
	r_e	r_0	E_e	E_0
C = C	1·350	1·353	131·6	129·1
C–C sp^2 sp^2	1·476	1·479	102·2	100·4
C–C sp^3 sp^3	1·540	1·543	82·5	83·9
C–H sp^2	1·071	—	—	100·9
C–H sp^3	1·095	—	—	97·2

Conjugation energies and resonance energies

With the values in Table 2, we can estimate the spurious "resonance energy" E_h of butadiene from equation (2):

$$E_h = (100{\cdot}4 - 83{\cdot}9) - 2(100{\cdot}9 - 97{\cdot}2) = 9{\cdot}1 \text{ kcal/mole} \qquad (21)$$

This value is actually *greater* than the experimental "resonance energy" of butadiene relative to two molecules of ethylene, which from heats of hydrogenation is found to be 8·1 kcal/mole. This implies that conjugation effects in butadiene are unimportant—in which case the central bond must be essentially a single bond, and its length (~1·46 Å) a measurement of r_1. The agreement with r_1 is within the limits of error claimed for the electron-diffraction measurements.

A further check was provided by a self-consistent treatment of butadiene by the method indicated above (equations (10) to (16)). The results were as follows:

Assumed initial values for bond lengths	1:2, 1·36 Å	2:3, 1·46 Å
Final self-consistent values	1:2, 1·359 Å	2:3, 1·445 Å

Calculated resonance energy, −0·5 kcal/mole.

These results provide useful confirmation of the argument in the previous paragraph; evidently conjugation alters the bond lengths and total energy very little—so that the length of pure single and double CC bonds must be close to those observed in butadiene. The discrepancy between theory and experiment is, however, serious; reasons will be given later for believing that the simple MO treatment, though excellent for aromatic molecules such as benzene or graphite, should be less successful for butadiene. Note that the resonance energy is *negative*. This negative "resonance energy" is

compensated by a greater decrease in σ-bond compression energy. Delocalisation occurs at all only in order to reduce the σ-bond compression energy, not because it is favourable in itself. The overall stabilisation is very small.

This argument is illustrated still more strikingly by benzene. The empirical "resonance energy" R is given by the difference in heat of hydrogenation between benzene and three molecules of ethylene:

$$R = 47{\cdot}9 \text{ kcal/mole} \tag{22}$$

Now a Kekulé structure for benzene contains three single bonds between sp^2 carbon atoms; the total spurious "resonance energy", R_h, due to hybridisation effects is given by:

$$R_h = 3 \times 8{\cdot}1 = 24{\cdot}3 \text{ kcal/mole} \tag{23}$$

The "true" resonance energy R_θ of benzene is then given by

$$R_\theta = R - R_h = 23{\cdot}6 \text{ kcal/mole} \tag{24}$$

But this still includes differential effects of σ-bond compression. The total compression energy of the σ bonds in three molecules of ethylene is 30·5 kcal/mole, that of the six σ bonds in benzene 19·7 kcal/mole. Therefore benzene is stabilised to the extent of 10·8 kcal/mole by the relief of σ-bond strain. Consequently the real resonance energy, R_π, of benzene, due to decrease in total π energy, is given by:

$$R_\pi = R_\theta - 10{\cdot}8 = 12{\cdot}8 \text{ kcal/mole} \tag{25}$$

In other words only about *a quarter* of the "observed resonance energy" of benzene is due to resonance; half is due to changes in bond energy of carbon bonds with hybridisation, and a quarter to the relief of σ-bond strain. The relief of strain is much greater than in the case of butadiene simply because the symmetrical structure of benzene allows a uniform sharing of π electrons—and so a uniformity of bond lengths—without *loss* of π energy.

"*Hyperconjugation*"

If resonance is unimportant in the ground state of butadiene, it must be completely unimportant in hyperconjugated structures such as propene. The "resonance energies" of such molecules must arise entirely from changes in bond energy with hybridisation [equations (3) to (5)]. This idea is supported very strongly by the data[9] in Table 3; the hyperconjugation energies of monoalkylethylenes are remarkably constant, and the mean hyperconjugation energies of both *sym*- and *as*-dialkylethylenes are in each case almost exactly double the value for monoalkylethylenes. It certainly seems very reasonable to ascribe the hyperconjugation energy (HCE) to a hybridisation effect [equation (5)].

We may take the mean hyperconjugation energy per alkyl group to be 2·3 kcal/mole. Hence from equation (5):

$$E''_{CC} = E_{CC} + (E'_{CH} - E_{CH}) + E'_h = 89{\cdot}9 \text{ kcal/mole} \tag{25}$$

[9] G. B. Kistiakowsky, J. R. Ruhoff, H. A. Smith and W. E. Vaughan, *J. Amer. Chem. Soc.* **58**, 137, 146 (1936); M. A. Dolliver, T. L. Gresham, G. B. Kistiakowsky and W. E. Vaughan, *Ibid.* **59**, 831 (1937); M. A. Dolliver, T. L. Gresham, G. B. Kistiakowsky, H. A. Smith and W. E. Vaughan, *Ibid.* **60**, 440 (1938).

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TABLE 3.· HEATS OF HYDROGENATION[9] AND DERIVED HYPERCONJUGATION ENERGIES (HCE) OF OLEFINES (kcal/mole)

C_3H_7	32·58
$MeCH=CH_2$	30·12
$EtCH=CH_2$	30·34
$AmCH=CH_2$	30·14
$Pr^iCH=CH_2$	30·33
$Bu^tCH=CH_2$	30·34
$CH_2(CH=CH_2)_2$	2 × 30·40
$CH_2(CH=CH_2)(CH_2-CH=CH_2)$	2 × 30·26
Mean	30·29
Mean HCE	2·29

$Me_2C=CH_2$	28·34
$MeHC=CH_2$	28·49
$MePr^iC=CH_2$	28·00
$MePe^{n\prime\prime\prime}C=CH_2$	27·24
Mean	28·02
Mean HCE	4·56 = 2 × 2·28

trans-Butene-2	27·62
cis-Butene-2	28·57
Pentene-2	27·94
*cyclo*Hexene	28·59
*cyclo*Pentene	27·93
Mean	27·93
Mean HCE	4·65 = 2 × 2·32

The corresponding value for the bond length (equation (19)) is found to be:

$$(sp^2) - (sp^3) : 1{\cdot}523 \text{ Å} \qquad (27)$$

The value reported for the exocyclic C–C bond in toluene (1·51 Å) agrees with this within the limits of experimental error.

Conjugation and resonance

The arguments given above suggest that resonance is unimportant in a molecule such as a polyene or olefine for which only one classical (unexcited) structure can be written. The "evidence" commonly quoted for resonance in such systems can be better interpreted in terms of changes in bond properties with hybridisation.

A different situation arises in aromatic compounds, and in odd conjugated systems (ions, radicals, and compounds such as cyanin dyes, which are iso-conjugate with carbanions). Here the bonds have intermediate lengths and the molecules possess stabilities greater than one would expect on the basis of hybridisation changes alone.

It would appear, therefore, that a naive form of the resonance theory, in which excited structures are neglected, gives a good qualitative account of conjugated systems.

This conclusion conflicts with the results of direct calculations by the MO method, which require considerable delocalisation of the π electrons in polyenes and corresponding changes in the lengths of bonds. This discrepancy can be ascribed to a neglect of electron correlation.

Two types of correlation can be recognised in π-electron systems: correlation effects tending to keep electrons in different AO's, and correlation effects tending to keep electrons on opposite sides of the nodal plane. Only effects of the first kind are taken into account in normal SCF MO calculations, even if configuration interaction is included. Now the second type of correlation enables electrons more easily to occupy similar positions along the carbon chain; it is due to neglect of this effect that the integrals representing mutual repulsion of pairs of electrons occupying the same AO's are overestimated in the usual treatment. As a result the SCF MO method must overestimate the delocalisation of electrons along the chain, even if configuration interaction is included. The success of the Pariser–Parr treatment, and Moffitt's "atoms-in-molecules" treatment, are undoubtedly due to their correction of these integrals; in this way they allow implicitly for the second type of electron correlation. These treatments should lead to pictures of molecules in which electron delocalisation is greatly reduced: Berry[10] has indeed found that an atoms-in-molecules treatment of butadiene leads to a picture of the ground state which corresponds closely to complete fixation of the 1 : 2 and 3 : 4 double bonds.

This question could be resolved only by direct calculation of π-electron distributions and energies by treatments in which electron correlation is explicitly taken into account. The following intuitive argument does, however, suggest that an exact treatment will lead to a picture close to that given by simple resonance theory, i.e., one in which resonance effects are significant only in molecules for which more than one classical structure can be written; and it also explains the success of current MO theory in dealing with aromatics and odd conjugative systems as well as its failure in the "classical" conjugated systems for which only one resonance structure can be written.

Consider the four π electrons in butadiene, occupying the two lobes of the π orbital. Mutual repulsion will tend to keep them apart; we may therefore expect at any instant to find two in each lobe. The two electrons in a given lobe will repel each other; they will also tend to linger in the regions between nuclei where the nuclear field is strongest. Hence the most probable distribution of the electrons should be that indicated in Fig. 2(a); these correlation effects will therefore tend to make the π electrons congregate

[10] J. S. Berry, *J. Chem. Phys.* **26**, 1660 (1957).

in pairs in the terminal bonds—thus accentuating the difference between "single" and "double" bonds and making the molecule approach more closely its single classical structure.

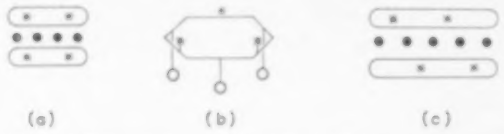

FIG. 2. Correlation diagrams for: (a) butadiene; (b) benzene; (c) the ion $C_5H_7^+$.

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Now consider benzene. Here again the π electrons are most likely to be evenly distributed between the two π lobes, and to occupy alternate bonds; but here the two sets can be staggered (Fig. 2b) so that there is an average one π electron per bond. Here correlation effects do not hinder delocalisation of the π electrons over all the bonds in the conjugated system. The same thing can happen in "odd" systems such as the pentadienate cation (Fig. 2c).

A little consideration will show that if the electrons in a given π lobe occupy alternate bonds, they must distribute themselves in accordance with a classical structure for the molecule. Therefore, if only one classical structure is possible, both sets of π electrons distribute themselves likewise, and this correlation effect makes the molecule approach the classical structure more closely than one would otherwise expect. If more than one classical structure can be written, the two sets of π electrons can conform to different structures, giving the effect of electron delocalisation. This provides an elegant explanation for the success of simple resonance theory.

Although these arguments have been applied to conjugated systems, they must also apply to systems which are hyperconjugated. One may therefore expect significant resonance effects due to hyperconjugation only in ions or radicals, when more than one unexcited (classical) structure can be written. The fact that some of these are "no-bond" structures does not matter; the total number of real bonds is the same in all. This is illustrated in Fig. 3 for the ethyl cation.

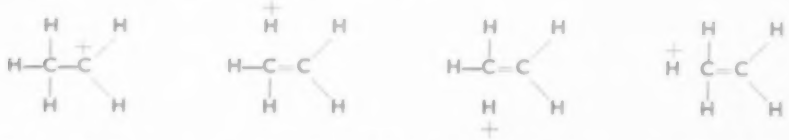

FIG. 3. Classical structures for the ion $C_2H_5^+$; note that in each case there are six real covalent bonds.

Conjugative stabilisation

The special chemical properties of benzene arise from its abnormally large heat of formation; this extra stability, compared with unconjugated analogues, is an experimental fact, and its efficacy is independent of its theoretical interpretation. The use of the term "resonance energy" for these experimentally measured quantities is therefore unsatisfactory, particularly since the argument given above suggest that only a small part of the extra heat of formation is due to resonance. It would be much better if the experimentally measured stabilisations were described as *stabilisation energies*, the term resonance energy being reserved for that part of the overall stabilisation that is due to delocalisation of electrons.

In most published work, "resonance energies" have been estimated by comparison with "reference compounds"; for example, the "resonance energy" of benzene is commonly given as the difference in heat of hydrogenation between three molecules of *cyclo*hexene and one of benzene. Our arguments indicate that this procedure is wrong in principle. A molecule such as *cyclo*hexene is conjugatively stabilised by the presence of bonds of a type (sp^2–sp^3) that are absent in benzene; the resonance energy found in this way is not only ambiguous (since it depends on the arbitrary choice of a reference compound) but it also contains irrelevant contributions from hyperconjugation in the reference compound. There will also be irrelevant steric effects, owing to conformational differences (e.g., between *cyclo*hexane and *cyclo*hexene).

Conjugation energy should be defined as the difference in heat of hydrogenation between the compound in question, and an appropriate number of molecules of simple compounds such as ethylene in which neither conjugation nor hyperconjugation is important. The same quantity can be calculated without difficulty from heats of combustion. Conjugation energies so defined are unambiguous and have an obvious chemical significance.

Further evidence for the effects of hybridisation

After the calculation described above had been completed, Bastiansen *et al.*[4] described a precision study of *cyclo*octatetraene by electron diffraction, leading to the bond lengths listed in Table 4.

TABLE 4. BOND LENGTHS (Å) IN ETHYLENE[3] AND *cyclo*OCTATETRAENE[4]

	C–C	C=C	C–H
Ethylene	—	1·334 ± 0·005	1·085 ± 0·005
*cyclo*octatetraene	1·462 ± 0·001	1·334 ± 0·001	1·090 ± 0·005

Now the bond angles in *cyclo*octatetraene preclude any significant resonance interaction between adjacent double bonds; the lengths of the CC bonds should therefore approximate closely to those of pure double and single bonds between sp^2 carbon atoms. The C=C bond length in fact agrees exactly with that found for ethylene by Bartell and Bonham[3]; but the value (1·462 Å) for the C–C bond is, if anything, *less* than that for the central bond in butadiene.

These results seem to provide unequivocal support for the argument developed in this paper. Moreover, the heat of hydrogenation of *cyclo*octatetraene agrees very closely with the value calculated from equation (1), using the bond energies listed in Table 2. It seems difficult to escape the conclusion that resonance effects are indeed unimportant in the ground state of butadiene.

The bond lengths for sp^2 carbon listed in Table 2 are, however, probably a little too large, owing to our assumption of the old value (1·353 Å) for the C=C bond. We are investigating this matter in detail; it seems unlikely that our general conclusions will be affected.

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POSSIBLE EFFECT OF HYPERCONJUGATION ON SOLVOLYSIS RATES OF BENZHYDRYL CHLORIDES* AND SPECTRA OF RELATED COMPOUNDS†

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Abstract—The near ultraviolet absorption spectra of a series of benz*cyclo*alkenes have been determined. A minimum in the absorption band near 270 mμ has been observed for benz*cyclo*heptene. It appears significant that this same inflexion occurs in the solvolysis rates for the related benzhydryl chlorides. The data indicate that hyperconjugation plays an important role, and an explanation is offered in terms of the Franck–Condon principle.

THE absorption band near 260 mμ in benzene is caused by the transition of a π electron. For reasons of symmetry, this transition is a so called forbidden transition, and leads to an absorption band of low intensity.[1]

Methyl substitution in benzene causes a shift towards longer wavelengths and brings about an intensification of this band. Molecular orbital calculations have led to the conclusion that the bathochromic shift of this O, O band results from hyperconjugation.[2] The intensification of the transition by alkyl groups is associated with a transition moment produced by a migration of charge into the benzenoid ring.[3, 4] According to Mulliken,[5] "this migration of unsaturation-electron charge implies hyperconjugation."

Furthermore, a decrease in wavelength, as well as in intensity, for the O,O band in alkylbenzenes follows the order: toluene, ethylbenzene, *iso*propylbenzene and *tert.*-butylbenzene. This order can be explained by a decrease in the contribution by hyperconjugation,[6] although an alternative explanation has been proposed.[7]

For reasons which are not completely understood at present, the effect of alkyl groups on the absorption in the near ultraviolet region by aromatic compounds is not consistent. For example, in contrast to the "hyperconjugative order" mentioned above for the aromatic hydrocarbons, the intensities of the absorption bands for *para*-alkyl-substituted nitrobenzenes and aromatic ketones follow an "inductive order" (i.e., *tert.*-butylbenzene > *iso*propylbenzene > ethylbenzene > toluene).[8]

* From the Ph.D. Thesis of W. R. Moore, University of Minnesota (June 1954).
† From the Ph.D. Thesis of Erich Marcus, University of Minnesota (June 1956).
‡ School of Chemistry, University of Minnesota.
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[1] H. Sponer, G. Nordheim, A. L. Sklar and E. Teller, *J. Chem. Phys.* **7**, 207 (1939).
[2] V. A. Crawford, *J. Chem. Soc.* 2061 (1953).
[3] A. L. Sklar, *J. Chem. Phys.* **10**, 135 (1940).
[4] A. L. Sklar, *Rev. Mod. Phys.* **14**, 232 (1942).
[5] R. S. Mulliken, *Rev. Mod. Phys.* **14**, 265 (1942).
[6] F. A. Matsen, W. W. Robertson and R. L. Chuoke, *Chem. Rev.* **41**, 273 (1947).
[7] V. J. Hammond, W. C. Price, J. P. Teegan and A. D. Walsh, *Disc. Faraday Soc.* **9**, 53 (1950).
[8] W. M. Schubert, J. Robins and J. L. Haun, *J. Amer. Chem. Soc.* **79**, 910 (1957), and earlier papers.

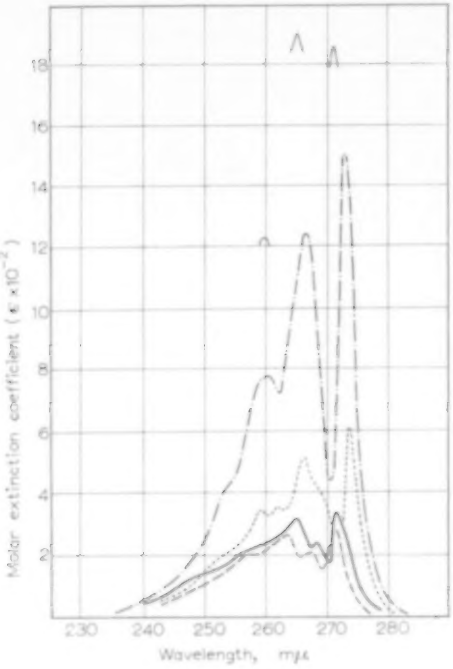


FIG. 1. Benz*cyclo*butene (peaks only) (——); benz*cyclo*pentene (– · – · –); benz*cyclo*hexene (· · · ·); benz*cyclo*octene (——); benz*cyclo*heptene (– – – –).

Of particular interest in the present study is the effect of cyclization on the absorption spectra of 1,2-dialkylbenzenes. Remart-Lucas and Hoch[9] compared the spectra of *o*-xylene and indan in the region near 270 mμ and concluded that the absorption bands for these two compounds—aside from mere fine structure—were essentially the same. This conclusion, referred to in later review articles,[10, 11] is not in agreement with our data, which show that the O,O band in indan (benz*cyclo*pentene) is some sevenfold more intense than that for *o*-xylene.

Table 1 summarizes pertinent absorption data for a series of 1,2-dialkylbenzenes (I) and Fig. 1 provides more detailed information on several of these.

I

[R,R = CH_3, CH_3; CH_3, C_2H_5, $C_6H_5(CH_2)_n$–]

It is apparent from Table 1 that all of the 1,2-benz*cyclo*alkenes which we have studied absorb more strongly near 270 mμ (i.e., the O,O transition) than does *o*-xylene. This same generalization holds also for the more highly substituted derivatives

[9] P. Remart-Lucas and M. J. Hoch, *Bull. Soc. Chim. Fr.* (5) **2**, 327 (1935).
[10] R. N. Jones, *Chem. Rev.* **32**, 28 (1943).
[11] G. Kortüm and G. Dreesen, *Chem. Ber.* **84**, 182 (1951).

TABLE 1. ULTRAVIOLET ABSORPTION OF 1,2-DIALKYLBENZENES (I)

Compound	λ_{max} (mμ)	ϵ_{max} (95% ethanol)	ϵ_{max} (*iso*octane)
$n = 2$	271	(1860)[12]	—
$n = 3$	273	1450	1500
$n = 4$	274	627	620
$n = 5$	271	292	277
$n = 6$	272	344	325
o-Xylene	271	—	(204), (212)[13]
o-Diethylbenzene	271	—	(200), (208)[14]

having substituents in the 1,2,4,5, positions.[15] In addition, it will be observed that the intensity of absorption drops rapidly from benz*cyclo*butene to benz*cyclo*heptene, and then a small but definite rise occurs for benz*cyclo*octene.

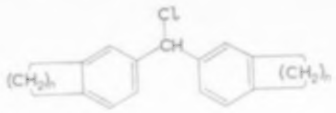
This inflexion, in the absence of other data, might not have been regarded as significant. We are intrigued, however, by the fact that this same inflexion has been found in the first-order solvolysis rates for the substituted benzhydryl chlorides (II), as shown in Table 2.*

TABLE 2. RELATIVE RATES OF SOLVOLYSIS (90% ACETONE) OF CHLORODIBENZ*cyclo*ALKENYLMETHANES (II)

n	Relative rates		Activation energy (kcal/mole)
	0°	25°	
3	2·94	2·42	16·4
4	1·62	1·56	17·3
5	1·00	1·00	17·6
6	1·25	1·19	17·3

* It is intended that the preparation of and kinetic data for these compounds will be given in detail in a subsequent article.

[12] M. P. Cava and D. R. Napier, *J. Amer. Chem. Soc.* **78**, 500 (1956).
[13] Amer. Petroleum Inst. Res. Project 44, Serial Nos. 43 and 55 (1945).
[14] Amer. Petroleum Inst. Res. Project 44, Serial Nos. 77 and 186 (1945, 1947).
[15] Erich Marcus, W. M. Lauer and R. T. Arnold, *J. Amer. Chem. Soc.* **80**, 3742, (1958).



II

It is possible, of course, that the inflexion which has been found to be a common feature of the above-mentioned spectral and rate studies may be fortuitous. We prefer, however, to believe otherwise. An examination of earlier published data,[6, 16, 17, 18]

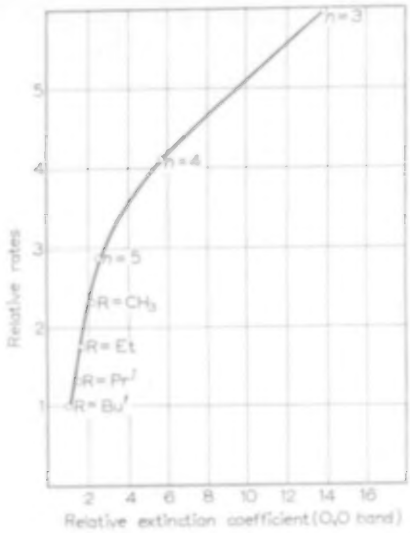
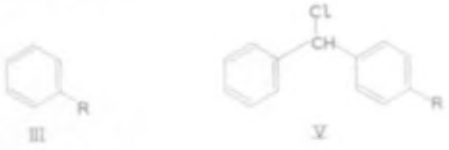


Fig. 2. Relative rates of hydrolysis of compounds (V) and (VI) (80% acetone, 0°) vs. relative molar extinction coefficients of related hydrocarbons (III) and (IV).

combined with some results from the present study, as shown in Fig. 2, suggests a relationship between the intensities of absorption (at peak nearest 270 mμ) of the hydrocarbons represented by (III) and (IV) and the solvolysis rates for the related benzhydryl chlorides (V) and (VI).



III V

IV VI

[16] E. D. Hughes, C. K. Ingold and N. A. Taher, *J. Chem. Soc.* 949 (1940).
[17] R. T. Arnold and W. L. Truett, *J. Amer. Chem. Soc.* 73, 5508 (1951).
[18] G. Baddeley and M. Gordon, *J. Chem. Soc.* 2190 (1952).

Although we recognize the importance of steric effects which may increase solvation energies[8, 19] and lead to a diminution in the solvolysis rates of benzhydryl chlorides, it should be pointed out that the variations found in Tables 1 and 2 can be rationalized in terms of steric factors which could determine, in large part, the extent to which hyperconjugation comes into play in these molecules.

DISCUSSION

Let us now consider in more detail the geometry of tetrahydronaphthalene and indan, because it is in these cases where the most significant change in extinction coefficients occurs. The ground state of tetrahydronaphthalene is represented by (*A*) and the partial (and exaggerated) formulae—which represent conformations—by (*B*) and (*C*), as follows:

A *B* *C*

Tetrahydronaphthalene, because of its "zig-zag" structure, has stable conformations (*B* and *C*) such that C_4 and C_5 are alternately above and below the plane of the ring and C_3 and C_6 are here assumed to be slightly above or below the plane of the ring, depending on the positions of C_4 and C_5.*

The excited state—in which hyperconjugation plays a more prominent role—is indicated below by formula (*D*) and a crude representation of the extreme conformations by (*E*) and (*F*) as seen from a point in the plane of the benzenoid ring:

D *E* *F*

In the excited state, it is expected that a stronger bond will exist at C_1–C_6 and C_2–C_3. For purposes of simplification, let us consider the C_{A_2}–C_{A_1} out-of-plane vibrations. Out-of-plane vibrations of the C_2–C_3 bond in the excited state should have a smaller amplitude than the same vibrations in the ground state. If a plot is made of the potential energy of this model against the angle (θ) of out-of-plane vibration, the picture shown in Fig. 3 will be obtained.

According to the Franck–Condon principle, the angle θ cannot be changed during an electronic transition. Therefore, the transition is forbidden for those molecules where $\theta > \theta_1$. The fraction of molecules that can make the transition is a factor in determining the transition probability and, therefore, the absorption band intensity.

In benz*cyclo*butene (1; $n = 2$), the conformations in the ground and excited states must be very similar. According to our view, this would account for the high absorption observed for this molecule, and leads us to predict a high rate of solvolysis for the corresponding benzhydryl chloride when it finally becomes available.

* We thank Dr. Bryce L. Crawford for stimulating and useful discussions on these points.

[19] C. C. Price and W. J. Belanger, *J. Amer. Chem. Soc.* **76**, 2682 (1954).

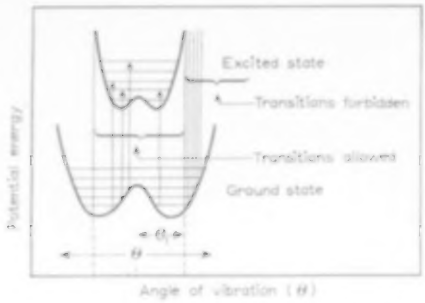


Fig. 3. Potential-energy diagram (qualitative) for tetrahydronaphthalene.

Although indan (I; $n = 3$) is not a completely planar molecule, we believe that the difference in the out-of-plane vibrations in the ground and excited states is much smaller than that in tetrahydronaphthalene, and that its potential-energy diagram may be qualitatively represented by Fig. 4.

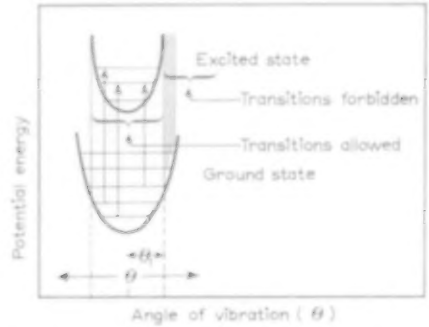
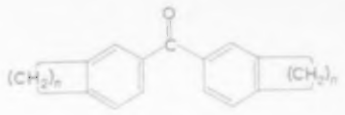


Fig. 4. Potential-energy diagram (qualitative) for indan.

Molecular models of the compounds reported on here do indicate an extreme out-of-plane position for the α-methylenic carbon atoms in benz*cyclo*heptene (I; $n = 5$), and an application of the above argument offers a reasonable explanation for the minima which we are reporting for spectral and rate data in this series.

Finally, a careful examination of Courtauld or Fischer–Hirshfelder–Taylor models for benz*cyclo*octene (I; $n = 6$) indicates that the molecule can assume many conformations, all of which involve a considerable degree of intramolecular crowding. Although it includes a great deal of speculation, we have concluded that the difference in the amplitude of the C_{A_r}–C_{A1} out-of-plane vibrations in benz*cyclo*octene in the ground and excited states should be smaller than that for benz*cyclo*heptene, and thus permit a greater probability of transition from ground to activated state. This, then, accounts for the interesting inflexion referred to earlier in this paper.

Schubert and co-workers[8] have pointed out, quite convincingly, the difficulty of explaining the spectra of *p*-alkylacetophenones on the basis of hyperconjugation. In the course of the present study, we examined the ultraviolet spectra for the benzophenone derivatives (VII), and the pertinent data are included in Table 3.



VII

(n=3,4,5,6)

TABLE 3. ULTRAVIOLET ABSORPTION OF DIBENZ*cyclo*ALKENYL KETONES (VII)

n	*iso*Octane (solvent)		95% Ethanol (solvent)	
	λ_{max} (mμ)	$\epsilon_{max} \times 10^{-2}$	λ_{max} (mμ)	$\epsilon_{max} \times 10^{-2}$
3	262	203	270	181
4	263	221	271	199
5	263	227	271	206
6	264	236	271	211

With respect to ring size vs. intensity of absorption, it will be seen (i) that the order followed in Table 1 is almost the reverse of that found in Table 3 and (ii) no inflexion occurs at $n = 5$ in Table 3. We are unable, at present, to explain these differences.

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HYPERCONJUGATION IN AROMATIC CATION COMPLEXES

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Abstract—Aromatic hydrocarbons react with the strong acid $HF–BF_3$ to form an aromatic cation plus the fluoroborate ion. The proton adds to a definite ring carbon atom and completely transfers its charge. The charge is distributed by resonance to positions *ortho* and *para* to the added proton. Alkyl groups on these positions stabilize the ion and distribute the charge further by hyperconjugation or induction. Thus, the mesitylene cation is more stable than the toluene cation by a factor of 280,000 and more stable than the other trimethylbenzenes by a factor of 70. Competition experiments among various 1, 3, 5-trialkylbenzene show no change in basicity as the alkyl groups vary from methyl to ethyl to *iso*propyl to *tert.*-butyl. In this series, therefore, the loss in carbon–hydrogen hyperconjugation is balanced by an increase in the induction effect and in carbon–carbon hyperconjugation.

Aromatic hydrocarbons, as is well known, form loose molecular complexes with many reagents, such as silver ion,[1] iodine[2] and hydrogen chloride.[3] The acceptor molecule combines loosely with the π-electron cloud of the aromatic ring. We have found[4] that alkylbenzenes also form mole-for-mole complexes with $HF–BF_3$. But, with this strong acid, the complexes are of an altogether different type. A proton adds to a definite ring carbon atom, completely transfers its charge to the aromatic hydrocarbon and thus brings into play inductive and hyperconjugative effects that do not show up in the π complexes.

Relative stability of complexes

Evidence for the existence of these complexes was obtained by measuring the vapor pressure of various mixtures of $HF–BF_3$ and aromatic hydrocarbons. One mole of the aromatic was stirred with 10 moles of liquid anhydrous HF in a closed system; because the aromatic and HF are immiscible two separate phases co-existed. Small amounts of BF_3 were added at intervals, and the pressure was measured after each addition.

The measurements are plotted in Fig. 1. The straight-line curve for BF_3 in HF alone shows that BF_3 in HF obeys Henry's law. No detectable amounts of HBF_4 are formed. The curves for hexamethylbenzene and mesitylene break sharply at the point where the mol ratio of BF_3 to aromatic equals one. As BF_3 is added, it reacts mole-for-mole with the aromatic until the aromatic is used up. Also, as the BF_3 is added, the hydrocarbon gradually dissolves in the HF layer and the mixture becomes homogeneous. Then the pressure rises abruptly and follows a line roughly parallel to that for $HF–BF_3$ alone.

The complex formed by mesitylene is less stable than that by hexamethylbenzene;

[1] L. J. Andrews and R. M. Keefer, *J. Amer. Chem. Soc.* **71**, 3644 (1949).
[2] H. A. Benesi and J. H. Hildebrand, *J. Amer. Chem. Soc.* **71**, 2703 (1949).
[3] H. C. Brown and J. Brady, *J. Amer. Chem. Soc.* **71**, 3573 (1949).
[4] D. A. McCaulay and A. P. Lien, *J. Amer. Chem. Soc.* **73**, 2013 (1951).

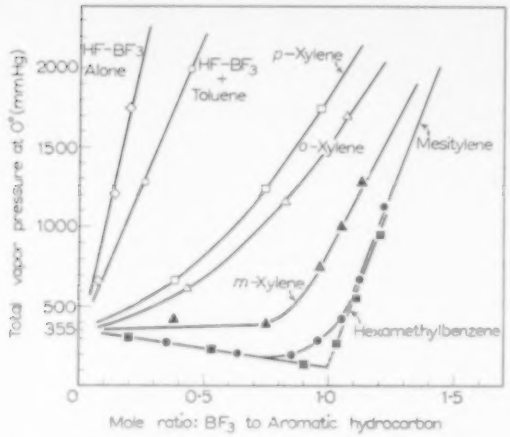


FIG. 1. Vapor pressures of mixtures of HF–BF_3 and aromatic hydrocarbons.

it exerts a slightly higher BF_3 pressure in the one-to-one region. The *m*-xylene complex is still less stable and approaches 100 per cent association only at relatively high BF_3 pressures. The complexes with *o*-xylene, *p*-xylene and toluene are progressively less stable.

The spread between the curve for the three xylene complexes permitted calculation of their relative stabilities. But, to get quantitative information for the other methylbenzenes required a series of batch extraction experiments in which the aromatics competed with each other for a limited amount of acid. In these experiments, two aromatics were dissolved in an inert paraffinic solvent, *n*-heptane, and were then shaken up with HF plus BF_3. The aromatic hydrocarbon that showed the greater tendency towards complex formation reacted preferentially and dissolved as a complex in the HF layer. A typical extraction run with mesitylene and *m*-xylene showed, in mol per cent:

	Feed	Raffinate	Extract
n-Heptane	50·0	75·0	0
Mesitylene	16·5	0·1	49
m-Xylene	33·5	24·9	51

Mesitylene was preferentially taken into the acid layer.

To measure this selectivity, single-stage separation factors, called α's, were calculated. They were defined as the mol ratios of the two components in the acid phase divided by the same mol ratio in the hydrocarbon phase. As a first approximation, we assumed that the ratio of the two aromatics in the hydrocarbon phase was equal to the ratio of free, uncomplexed aromatics in the acid layer. Then, the α value can be looked upon as the equilibrium constant for the reaction:

Table 1. Relative basicities of the methylbenzenes
p-Xylene = 1

Methylbenzene	α
Toluene	0·01
p-Xylene	1
o-Xylene	2
m-Xylene	20
Pseudocumene (1, 2, 4-)	40
Hemimellitene (1, 2, 3-)	(40)
Durene (1, 2, 4, 5-)	120
Prehnitene (1, 2, 3, 4-)	170
Mesitylene (1, 3, 5-)	2,800
*iso*Durene (1, 2, 3, 5-)	5,600
Pentamethylbenzene	8,700
Hexamethylbenzene	89,000

$$A_1H^+ + A_2 \rightleftharpoons A_2H^+ + A_1 \qquad \alpha = K = \frac{[A_2H^+]\,[A_1]}{[A_1H^+]\,[A_2]}$$

in which the two aromatics compete for a proton. For this reason, it is called the relative basicity of the two aromatics.

Experiments were carried out for all of the methylbenzenes, and the α values obtained were arranged in Table 1. Basicity increases with the addition of each methyl group. The xylenes are more basic than toluene; the trimethylbenzenes more basic than the xylene. But *meta* orientation contributes most to basic character. Thus, *m*-xylene is by far the most basic of the xylenes. Likewise, mesitylene, with three *meta*-oriented groups, is far more basic than its isomers. In fact, it is more basic than two of the tetramethylbenzenes, which have only two *meta*-oriented groups.

Table 2. Basicities toward various reagents

Methylbenzene	Ag^{+}*	HCl †	I_2 ‡	$HF–BF_3$ §
Toluene	1·02	0·92	0·97	0·01
p-Xylene	1·00	1·00	1·00	1
o-Xylene	1·10	1·13	1·01	2
m-Xylene	1·15	1·26	—	20
Mesitylene	0·69	1·59	1·06	2800

* Solubility of arene in aqueous Ag^{+}.[1]
† Solubility of HCl in arene.[2]
‡ Light absorption.[2]
§ Competitive extraction.[4]

The relative basicity values obtained by use of this strong acid are compared in Table 2 with those obtained by others using weak electrophilic reagents. With the weak acids the spread from toluene through metitylene is small, in no case being greater than twofold. In contrast, the spread as measured by the strong acid, $HF–BF_3$, is about 280,000-fold. The strong acid completely transfers its charge to the aromatic

ring so that hyperconjugative and inductive effects are more important than they are in π complexes formed by the weaker acids.

Nature of the complexes

The best interpretation of the reaction of complex formation is:

$$A + HF \rightleftharpoons A \cdot H^+ + F^-$$
$$F + BF_3 \rightleftharpoons BF_4^-$$
$$\overline{A + HF + BF_3 \longrightarrow A \cdot H^+ + BF_4^-}$$

When the aromatic is added to HF alone, the equilibrium for the top reaction lies far to the left, as shown by the fact that aromatics are only slightly soluble in HF. However, when BF_3 is present, the reaction goes to completion because the stable fluoroborate ion is formed. For this reason 1 mole of BF_3 interacts with 1 mole of aromatic, as was observed in the vapor-pressure and batch-extraction experiments.

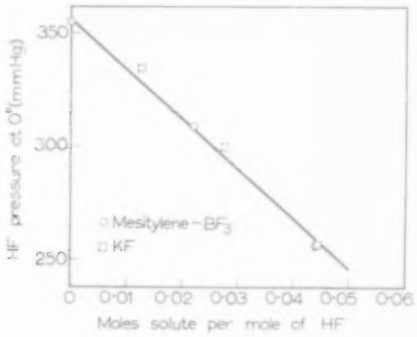


FIG. 2. Vapor-pressure lowering of HF by added KF or mesitylene–BF_3.

$$KF + HF \longrightarrow K^+ + HF_2^-$$
$$\text{Mesitylene} + BF_3 + HF \longrightarrow \text{Mesitylene} \cdot H^+ + BF_4^-$$

TABLE 3. COMPARISON OF CONDUCTIVITIES AND RELATIVE BASICITIES

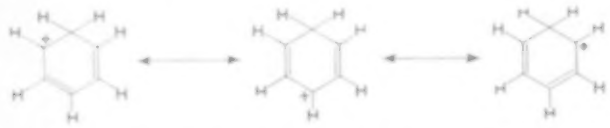
Methylbenzene	Relative conductivity in HF[5]	Relative basicity in HF–BF_3[4]
p-Xylene	1	1
o-Xylene	1·1	2
m-Xylene	26	20
Pseudocumene (1, 2, 4-)	63	40
Hemimellitene (1, 2, 3-)	69	40
Durene (1, 2, 4, 5-)	140	120
Prehnitene (1, 2, 3, 4-)	400	170
Mesitylene (1, 3, 5-)	13,000	2800
*iso*Durene (1, 2, 3, 5-)	16,000	6500
Pentamethylbenzene	29,000	8700
Hexamethylbenzene	97,000	89,000

[5] M. Kilpatrick and F. E. Luborsky, *J. Amer. Chem. Soc.* **75**, 577 (1953).

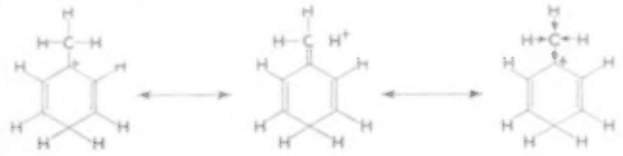
More evidence supporting the theory that one molecule of aromatic and one of BF_3 gives two ions instead of an ion pair or a single addition complex is shown in Fig. 2. Incremental amounts of a solute, either KF or an equimolar mesitylene–BF_3 mixture, were added to HF at 0°C, and the vapor pressure was measured. The points for both KF and for mesitylene–BF_3 fall along the same straight line, showing that they both give the same molal vapor-pressure lowering. If KF forms two particles in solution, then mesitylene–BF_3 must also do the same.

Conclusive evidence that these particles are charged was obtained from measurements of the conductivities of small amounts of the methylbenzenes dissolved in HF.[5] From these measurements were calculated values proportional to the equilibrium constants for the acid–base reaction. These values are shown in the first column of Table 3; our values, in the second column. The two sets of figures are in good agreement, considering that in our work we used concentrations of aromatic in HF that were about fifty-fold greater than in the conductivity studies.

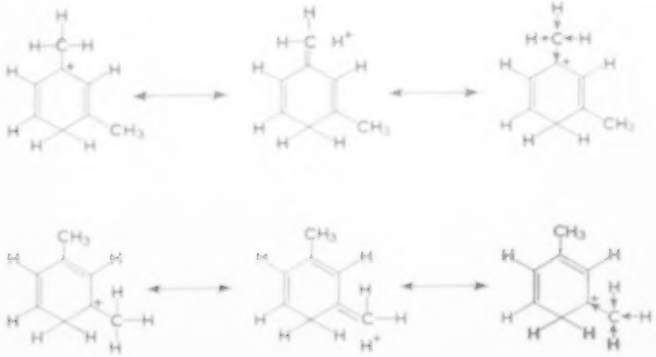
The probable structure of the aromatic cation is:



Presumably the proton adds directly to a ring carbon atom and the positive change is distributed to the *ortho* and *para* positions by resonance. If one of these positions has an alkyl substituent, the positive charge can be further distributed and stabilized by hyperconjugation or induction, as shown for the toluene cation:



The arrows represent displacement of the bonding pair, under the influence of the positive charge, from their normal position in the neutral molecule. Also, if the aromatic has another alkyl group in the *meta* positon, as does *m*-xylene, the charge can be further distributed, by induction and hyperconjugation, to both alkyl groups:



Mesitylene, with three *meta*-oriented groups, can stabilize and distribute the positive charge to all three alkyl groups.

Effect of change of alkyl group on basicity

Some idea of the relative contributions of the inductive and hyperconjugative effect in stabilizing the cation could be obtained by comparing methyl substituents with ethyl, *iso*propyl and *tert.*-butyl groups. But a direct comparison has not previously been possible because alkyl groups larger than methyl migrate rapidly from one ring to another in the presence of $HF–BF_3$. We have recently found, however, that the 1,3,5-trialkylbenzenes are exceptionally stable in $HF–BF_3$ and that they maintain their configuration long enough for an extraction experiment to be made.

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Therefore, a series of competitive extraction experiments was run with 1,3,5-trialkylbenzenes containing methyl, ethyl, *iso*propyl and *tert.*-butyl groups. Two 1,3,5-trialkylbenzenes dissolved in *n*-heptane were shaken up with HF plus enough BF_3 to complex with about one-half of the total aromatic present. The hydrocarbon phase and the acid layer were then separated and were analyzed by gas chromatography. A single-stage separation factor, α, was calculated for each pair.

TABLE 4. APPARENT BASICITY OF THE 1, 3, 5-TRIALKYLBENZENES

1, 3, 5-Trialkylbenzene	α
1, 3, 5-Tri-*tert.*-butylbenzene	1·0
1-Methyl-3, 5-di-*tert.*-butylbenzene	2·8
1, 3, 5-Tri*iso*propylbenzene	4·8
1-Methyl-3, 5-di*iso*propylbenzene	6·0
1, 3, 5-Triethylbenzene	8·4
1, 3-Dimethyl-5-*tert.*-butylbenzene	15·5
1, 3-Diethyl-5-methylbenzene	16·8
1, 3-Dimethyl-5-*iso*propylbenzene	20·2
1, 3-Dimethyl-5-ethylbenzene	30·7
1, 3, 5-Trimethylbenzene	54·4

The α values obtained were arranged in order in Table 4. The basicity apparently increases with decreasing branching in the side-chain. As the methyl segments of the tertiary butyl groups are replaced by hydrogen atoms, the α values become larger. The effect on apparent basicity is in the order: methyl > ethyl > *iso*propyl > *tert.*-butyl. Carbon–hydrogen hyperconjugation, therefore, appears to contribute more than induction or carbon–carbon hyperconjugation. But before this conclusion can be accepted a correction must be made. The equilibrium constant for the acid–base reaction in the HF layer is:

$$A_1H^+ + A_2 \rightleftharpoons A_2H^+ + A_1 \qquad K = \frac{[A_2H^+]\,[A_1]_{HF}}{[A_1H^+]\,[A_2]_{HF}}$$

But the single-phase separation factor, α, is:

$$\alpha = \frac{[A_2H^+]\,[A_1]_{\text{Heptane}}}{[A_1H^+]\,[A_2]_{\text{Heptane}}}$$

Therefore:

$$K = \alpha \frac{[A_1]_{HF}[A_2]_{Heptane}}{[A_2]_{HF}[A_1]_{Heptane}}$$

The ratio between the uncomplexed hydrocarbons, $[A_1]$ and $[A_2]$, in the acid phase can be estimated from the solubilities of the free uncomplexed hydrocarbons in HF:

$$\frac{[A_1]_{HF}}{[A_2]_{HF}} = \frac{[A_1]_{Heptane}}{[A_2]_{Heptane}} \times \frac{\text{Solubility of } A_1 \text{ in HF}}{\text{Solubility of } A_2 \text{ in HF}}$$

and, therefore:

$$K = \alpha \times \frac{\text{Solubility of } A_1 \text{ in HF}}{\text{Solubility of } A_2 \text{ in HF}}$$

Direct measurement of the physical solubility of these highly basic aromatics in HF is not possible because most of the aromatic that goes into the HF layer is in the protonated form:

$$A \text{ (liquid)} \rightleftharpoons [A]_{HF} + [A \cdot H^+]$$

Recently, however, Mackor *et al.*[6] showed that a good estimate of the concentration of free uncomplexed aromatic in HF, $[A]_{HF}$, could be obtained from an extrapolation of the solubilities of less basic aromatics in HF. The logarithms of the solubilities of benzene, toluene and xylene in HF at 0° differ by a constant, 0·20, as shown by the following values:

Aromatic	Benzene	Toluene	*p*-Xylene	*m*-Xylene
Log (*A*)	1·35	1·55	1·76	1·72

Solubilities of the heavier alkylbenzenes were estimated by assuming that the value of log $[A]$ decreases by 0·2 for each additional methyl group on the ring. The values of 0·4, 0·6 and 0·8 were used for the corresponding ethyl, *iso*propyl and *tert*.-butyl groups.

Table 5. Corrected relative basicities

1, 3, 5-Trialkylbenzene	α	− Log (*A*)	Corrected relative basicity, *K*
1, 3, 5-Tri-*tert*.-butylbenzene	1·0	3·75	1·0
1-Methyl-3, 5-di-*tert*.-butylbenzene	2·8	3·15	0·8
1, 3, 5-Tri*iso*propylbenzene	4·8	3·15	1·4
1-Methyl-3, 5-di*iso*propylbenzene	6·0	2·75	1·2
1, 3, 5-Triethylbenzene	8·4	2·55	0·6
1, 3-Dimethyl-5-*tert*.-butylbenzene	15·5	2·55	1·1
1, 3-Diethyl-5-methylbenzene	16·8	2·35	0·7
1, 3-Dimethyl-5-*iso*propylbenzene	20·2	2·35	0·9
1, 3-Dimethyl-5-ethylbenzene	30·7	2·15	0·9
1, 3, 5-Trimethylbenzene	54·4	1·95	1·0

[6] E. L. Mackor, A. Hofstra and J. H. Van Der Waals, *Trans. Faraday Soc.* **54**, 186 (1958).

Solubilities for all the 1,3,5-trialkylbenzenes in HF were calculated by this means and are shown in Table 5. These values were substituted in the equation relating π to K, the corrected relative basicity. The K values so calculated are shown in the last column. No trend is observed as the alkyl group changes. In going from methyl to ethyl to *iso*propyl to *tert.*-butyl, the loss in carbon–hydrogen hyperconjugation apparently is balanced by an increase in the inductive effect and in carbon–carbon hyperconjugation.

Carbon–hydrogen hyperconjugation, therefore, must be an important mode of electron release in the methyl-substituted cations. If only the inductive effect were involved, an increase in basicity would be expected with an increase in size and branching of the alkyl substituent.

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ROLE OF SOLVENT IN ALKYL SUBSTITUENT EFFECTS

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Abstract—From the energies of electronic transitions that place a high electron demand on alkyl substituents (e.g., the "principal" transition of *p*-alkylnitrobenzenes in the gas phase) it is concluded that the inherent order of electron release is: $Bu^t > Pr^i > Et > Me$. For RCH_2 groups larger spreads are found, in the release order: $Pe^{neo} > Bu^t > Pr > Et > Me$. A Baker–Nathan effect has been found in the principal electron-transition energies of *p*-alkylnitrobenzenes and *p*-alkylacetophenones in basic solvents. This effect is attributed to steric hindrance to solvation of the electron-deficient aromatic ring in the vicinity of the alkyl substituent.

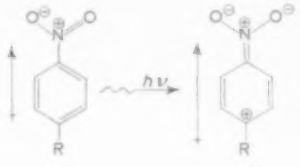
In electronic transitions of the type in which a substituent is called upon strongly to accept negative charge (e.g., the "principal" transition of *p*-alkylphenols in the gas phase) it has been found that alkyl groups are apparently better electron *acceptors* than a hydrogen.

Rate constants and heats and entropies of activation obtained in the solvolysis of 3,5-dimethyl- and 3,5-di-*tert*.-butyl-benzhydryl chlorides are compared with corresponding results on mono *m*- and *p*-alkylbenzhydryl chlorides. The assumption that the Baker–Nathan effect in this system is due to a C–H hyperconjugative order of electron release by alkyl groups does not satisfactorily account for the results. On the other hand, the results are completely consistent with the viewpoint that the Baker–Nathan effect is due to steric hindrance to solvation of electron-deficient sites in the near vicinity of the alkyl substituent.

IT has been pointed out recently that the original theory of Baker and Nathan[1] is unable to embrace many facts apparently within its proper province, and three suggestions for modification or replacement of the theory appeared practically simultaneously.[2, 3, 4] Sweeney and Schubert have suggested that even in the face of a high electron demand, the inherent electron release by alkyl groups may still be in the inductive order. It was not concluded that C–H hyperconjugation is necessarily inoperative; only that, *if* it is operative, other release modes in the inductive order (i.e., the inductive effect and possibly C–C hyperconjugation) may still predominate when alkyl is attached to a highly electron-deficient unsaturated system.[5] An inversion in the order of experimental quantities such as rate and equilibrium constants; i.e., the Baker–Nathan effect is then ascribed to steric hindrance to solvation of electron-deficient sites in the near proximity of the alkyl group.[3] Earlier, Price and Lincoln had suggested that a bulky group such as Bu^t may shield the direct reaction site from solvation.[6] Shiner has suggested that the role of the solvent is to enhance C–H over C–C hyperconjugation, by incipient hydrogen-bonding of the solvent with the α hydrogens of the alkyl substituent.[2] Burawoy and Spinner have chosen to neglect the role of the solvent, except possibly insofar as it may act to change the demand for electrons placed upon the alkyl group. They consider the Baker–Nathan effect to be caused by steric hindrance to bond shortening, with the alkyl groups releasing only by the inductive mechanism.[4]

[1] J. W. Baker, *Hyperconjugation*. Oxford University Press (1952).
[2] V. J. Shiner, Jr., *J. Amer. Chem. Soc.* **76**, 1603 (1954).
[3] W. A. Sweeney and W. M. Schubert, *J. Amer. Chem. Soc.* **76**, 4625 (1954).
[4] A. Burawoy and E. Spinner, *J. Chem. Soc.* 3752 (1954).
[5] W. M. Schubert and W. A. Sweeney, *J. Org. Chem.* **21**, 119 (1956).
[6] C. C. Price and D. C. Lincoln, *J. Amer. Chem. Soc.* **73**, 5836 (1951).

Contradiction to the original theory is found mainly in the energies of transitions of the type in which the Franck–Condon principle applies, i.e., electronic transitions.[6] A specific example is seen in the data of Table 1, which gives the energies the so called principal band transition of *p*-alkylnitrobenzenes and *p*-alkylacetophenones *in the gas phase*. The principal band (also called *K*-band) has been identified as due to a dipolar transition in the long axis of the molecule. It is approximately described by the valence-bond structures (I) and (II), which are representative of the ground and excited states, respectively.[7]



(I) (II)

TABLE 1. VALUES OF $\nu_R - \nu_{Me}$ ($cm^{-1} \pm 30\ cm^{-1}$) FOR THE PRINCIPAL BAND OF *p*-ALKYLNITROBENZENES AND *p*-ALKYLACETOPHENONES IN THE GAS PHASE[8, 9]

R=	H	Me	Et	Pr^i	Bu^t
p-$RC_6H_4NO_2$	+1850	0*	−130	−180	−210
p-$RC_6H_4COCH_3$	+1370	0†	−110	−140	−160
p-$RCH_2C_6H_4NO_2$	0*	−130	−220	−370	−480

* Nitrotoluene has $\nu_{max} = 39970\ cm^{-1}$.
† *p*-Methylacetophenone has $\nu_{max} = 41860\ cm^{-1}$.

For the series R, rows 1 and 2 of Table 1, it is seen that the stabilization of the highly electron-demanding excited state relative to the ground state takes the order: Bu^t > Et > Me ≫ H.[8] The excitation energy of the *iso*propyl compound of either series lies between those of the corresponding *tert.*-butyl and ethyl compounds, but is within experimental error of the *tert.*-butyl compound in the nitrobenzene series and of both the ethyl and *tert.*-butyl compounds in the acetophenone series. It is concluded from these gas-phase results that the *inherent* order or electron release is the inductive one, at least in these electronic transitions. The order of electron release in the series RCH_2, row 3 of Table 1, is: Pe^{neo} > Bu^t > Pr > Et > Me.[9] Furthermore, *neo*pentyl is inherently a more efficient electron-releasing group than either methyl or *tert.*-butyl. Therefore, steric inhibition of hyperconjugation[10, 11, 12] is not important in the electron-release effects of the alkyl groups, at least for these systems.*

* The "extra" activating effect of the *neo*pentyl group and the relatively large spreads in excitation energy for the series RCH_2 may mean that, in addition to a polarization through the bond to the substituent, there is a direct polarization across space by the electron-deficient ring of that portion of the alkyl group that closely overhangs the ring.[9]

[7] W. T. Simpson and A. G. Albrecht, *J. Amer. Chem. Soc.* **77**, 4455 (1957), and preceding papers.
[8] W. M. Schubert, J. Robins and J. L. Haun, *J. Amer. Chem. Soc.* **79**, 910 (1957).
[9] W. M. Schubert and J. Robins, *J. Amer. Chem. Soc.* **80**, 559 (1958).
[10] V. H. Shiner, Jr., *J. Amer. Chem. Soc.* **78**, 2654 (1956).
[11] R. T. Arnold and W. L. Truett, *J. Amer. Chem. Soc.* **73**, 5508 (1951).
[12] G. Baddeley and M. Gordon, *J. Chem. Soc.* 2191 (1952).

The effect of a wide variety of solvents on the principal band transition energy of both R series of Table 1 and of *p-neo*pentylnitrobenzene has been determined.[8, 9] The important result is that the Baker–Nathan effect was observed in basic solvents. That is, for the R series of both the nitrobenzenes and acetophenones, basic solvents (water was the most effective) gave a jumbled order of excitation energies tending toward a complete Baker–Nathan order. The spread in excitation energy between *p-neo*pentyl- and *p*-methyl-nitrobenzene also was noticeably reduced in basic solvents (e.g., $\nu_{Me} - \nu_{Pe^{neo}} = 270\ cm^{-1}$ in *n*-butylamine). From these results, it was concluded that at least for these electron transitions, the Baker–Nathan effect is not caused by an inversion in the *inherent* inductive *order* of electron release but is due to an indirect solvent effect. Explanation of these results can be found in terms of steric hindrance to solvation of electron-deficient sites in the near vicinity of the alkyl group. Even though practically no movement of solvent molecules is allowed in the short time of the electronic transition (Franck–Condon principle), solvent stabilization by basic species at electron-deficient sites in the ring should be greater in the excited state than in the ground state of this particular transition.[8, 9] The bulkier the alkyl substituent, then, the greater would be interference with solvent stabilization of the excited state relative to the ground state, and hence the less would be the solvent lowering of the excitation energy.* An equally satisfactory qualitative explanation of these solvent effects can be found in terms of Shiner's idea of solvent enhancement of C–H hyperconjugation, provided it is assumed that there is steric hindrance to solvation of the α hydrogens of the *neo*pentyl group. However, steric hindrance to ring solvation appears to give a more satisfactory explanation of the results of a quantitative treatment of the solution data made in terms of a linear free-energy relationship.[7, 8] Thus there is found a very good linear proportionality between solvent effects for Me vs. H compounds, but a relatively poorer proportionality between solvent effects for Bu^t vs. H and Pe^{neo} vs. H.[8, 9]

In a search for possible direct evidence for solvent enhancement of C–H hyperconjugation, a comparison of the principal band excitation energies of *p*-trideuteromethyl- and *p*-methyl-nitrobenzene has been made. The results obtained are given in Table 2.

TABLE 2. EXCITATION ENERGY SPREADS ($\pm$ 15 cm^{-1}) FOR *p*-NITROTOLUENES

	Heptane	Bu^nNH_2	Bu^tOH	Dioxan	95% EtOH	H_2O	52% $HClO_4$	96% H_2SO_4	70% $HClO_4$
$\nu_H - \nu_{CH_3}$	1810	1920	1960	2090	2090	2280	2480	2710	2750
$\nu_{CD_3} - \nu_{CH_3}$	50	40	40	30	30	50	60	70	70

The $\nu_{CD_3} - \nu_{CH_3}$ spreads show no detectable tendency predictable on the basis of solvent enhancement of C–H hyperconjugation; i.e., the spreads are not markedly altered in basic solvents of the type most likely to be involved in incipient hydrogen bonding at the α hydrogens (deuteriums). The only discernible trend is a slight increase in $\nu_{CD_3} - \nu_{CH_3}$ in more acidic solvents. This indicates that the methyl group

* The Baker–Nathan effect, although frequently observed in chemical transitions in solution, is rarely observed in electronic transitions in solution. This can be attributed to the fact that, owing to the Franck–Condon principle, the excited electronic states are not maximally solvated.

has a slightly larger absolute value of the Hammett σ constant than the CD_3 group. In fact, a plot of $\nu_{CH_3} - \nu_H$ vs. $\nu_{CD_3} - \nu_H$ with changing solvent gives a line with a slope, $\sigma_{Me}/\sigma_{CD_3}$, of 1·036 ± 0·002 and a correlation coefficient of $r = 0{\cdot}999$.

TABLE 3. VALUES OF $\nu_R - \nu_{Me}$ ($cm^{-1} \pm 20\ cm^{-1}$) FOR THE PRINCIPAL BAND OF 4-ALKYLPYRIDINIUM IONS IN 1% $HClO_4$ AND 4-ALKYL-1-HYDROXYPYRIDINIUM IONS IN 9% $HClO_4$

Series R, R =	H	Me	Et	Pr^i	Bu^t
4-$RC_5H_4NH^+$	+3820	0*	−430	−650	−900
4-$RC_5H_4NOH^+$	+1680	0†	−250	−350	−480
Series RCH_2, R =	**H**	**Me**	**Et**	**Pr^i**	**Bu^t**
4-$RCH_2C_5H_4NH^+$	0*	−430	−860	—	−1910
4-$RCH_2C_5H_4NOH^+$	0†	−250	−510	—	−1160

* 4-Methylpyridinium ion has $\nu_{max} = 46{,}080\ cm^{-1}$.
† 4-Methyl-1-hydroxypyridinium ion has $\nu_{max} = 44{,}000\ cm^{-1}$.

The effect of alkyl substitution upon the energy of the principal electronic transition of a number of positive ions in solution has been determined. The most complete series studied are the 4-alkylpyridinium ions and 4-alkyl-1-hydroxypyridinium ions. Excitation-energy data for the pyridinium ions in 1 per cent $HClO_4$ and the 1-hydroxypyridinium ions in 9 per cent $HClO_4$ are given in Table 3. Qualitatively, the effects of alkyl substitution in these solution spectra is the same as for nitrobenzene and acetophenone in the gas phase. That is, the series R follows the inductive order of excitation energies, and the same order of excitation energies is followed by the series RCH_2 as by the series R. The spreads in the excitation energy data of Table 3 are quite large. Note also that the larger H–Me spread for the pyridinium ions compared to the 1-hydroxypyridinium ions is associated with a larger spread among the alkyl compounds.* The effects of changing solvent also has been studied, although the types of solvents that can be used with these ions is somewhat limited. The solvent shifts are small and the same qualitative order of excitation energies was observed in all solvents used. The pyridinium ion spectra moved slightly to lower energies as solvent basicity was decreased, while the hydroxypyridinium ion spectra moved slightly to higher energies. An approximate balance between solvent stabilization of ground and excited states is indicated by the smallness of the solvent shifts. This is not surprising in view of the fact that the excitation involves a redistribution of positive charge (equation (2) is a crude valence bond representation of this transition); i.e., the decrease in solvent stabilization at sites decreasing in positivity on excitation is

* Large wavelength spreads, in the inductive order, also are seen in the spectra of a number of *p*-alkyldi- and *p*-alkyltri-arylmethyl carbonium ions in concentrated sulfuric acid. For example, the principal band of di-(*p-tert.*-butylphenyl)methyl carbonium ion lies 8 mμ above that of the dimethyl homologue.[13] However, at the high wavelengths of these principal bands, the spread in frequency is only 350 cm^{-1}.

[13] N. C. Deno, J. J. Jaruzelski and A. Schriesheim, *J. Org. Chem.* **19**, 155 (1954); *J. Amer. Chem. Soc.* **77**, 3044 (1954).

(3)

approximately balanced by the increase in solvent stabilization at sites increasing in positivity. The fact that the solvent shifts are small indicates that the order of excitation energies observed here probably represents the inherent order of electron release by the alkyl substituents in these transitions. The same trends, with less complete series, are also found in the principal band spectra of the conjugate acids of *p*-alkylacetophenones in concentrated sulfuric acid solution and *p*-alkylnitrobenzenes in fuming sulfuric acid.

Alkyl groups as acceptors of negative charge

It was deemed of interest to determine the effect of alkyl substituents in an electronic transition in which the substituent is called upon strongly to accept electrons. Such a transition is the "principal" electronic transition of phenol, anisole, aniline and dimethylaniline, represented approximately by equation (3). Results for the *p*-hydrogen, *p*-methyl and *p-tert.*-butyl compounds in the gas phase at 100–150° are given in Table 4.

TABLE 4. VALUES OF λ_{max} (mμ) FOR THE PRINCIPAL ELECTRONIC BAND OF PHENOLS, ANISOLES, ANILINES AND N N-DIMETHYLANILINES*

	H	Me	Bu^t
Z = OH	206·3	216·1	216·0
Z = OCH_3	215·0	219·8	219·9
Z = NH_2	229·4	233·7	232·7
Z = NMe_2	241·8	243·5	244·5

* The band position is unchanged over a temperature range of 100–150°.

Somewhat surprisingly, it is seen that the excitation energies of the *para*-methyl and *para-tert.*-butyl compounds lie below those of the parent *para*-hydrogen compound in each case. No significance should be attached to the relative λ_{max} values for the principal band of methyl and *tert.*-butyl compounds, since the principal bands are somewhat asymmetric, owing evidently to a near-lying lower wavelength transition. However, the principal band for each alkyl compound clearly lies at longer wavelengths than that of the corresponding hydrogen compound. In view of the nature of the transition, these results imply that alkyl groups are better electron *acceptors* than hydrogen when called upon strongly to accept electrons. This suggests that an alkyl group is more readily polarized than hydrogen when attached to a highly electron-

rich system as well as when attached to an electron-deficient system.[9, 14] In general, when an alkyl substituent is called upon to accept electrons in a chemical transition, it apparently does so less readily than hydrogen. Examples include the base catalyzed hydrolysis of ethyl *p*-alkylbenzoates* [15] and activated nucleophilic aromatic substitution.[16] It seems likely that the substituent is not called upon to accept negative charge as strongly as in the above-mentioned electronic transitions. It has been suggested that the ability of the substituent to accept negative charge is a function of both its electronegativity and its polarizability.[9, 14] Presumably hydrogen as a substituent is more electronegative than alkyl but less polarizable. In that event, it is possible that in the chemical transitions the qualitative order of electron acceptance is governed primarily by the electronegativity of the substituent, whereas in the electronic transitions it is governed primarily by the polarizability of the substituent.

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The Baker–Nathan effect in chemical transitions

It remains to be seen whether conclusions made about alkyl substituent effects in electronic transitions can be extrapolated to chemical transitions. The assumption made originally by Baker and Nathan, that alkyl groups release electrons in the C–H hyperconjugative order in the face of a high electron demand, is consistent primarily only with solution rate and equilibrium data.[5] However, if it is assumed that alkyl electron release is in the inductive order, whether the demand for electrons be low or high, the idea that steric hindrance to solvation of electron-deficient sites attached to the alkyl group acts to give the Baker–Nathan effect is consistent with a wide variety of both physical and chemical data on alkyl compounds.

TABLE 5. SOLVOLYSIS OF *p*-$RC_6H_4CHClC_6H_5$ IN "80%" ACETONE[17]

R =	H	Me	Et	Pr^i	Bu^t
$k \times 10^6$ sec^{-1} (0°)	2·82	83·5	62·6	46·0	35·9
$\Delta H^{\ddagger}$	20·5	18·3	18·9	19·3	19·5
$\Delta S^{\ddagger}$	−8·9	−9·8	−8·6	−7·7	−5·6

As a typical example of the kind of observation on which the theory of Baker and Nathan is based, consider the solvolysis of *p*-alkylbenzhydryl halides in "80%" acetone (Table 5). Both the rate constants and heats of activation show a Baker–Nathan effect. This is of course consistent with the conclusion that inherent release by the alkyl groups in this transition is in the C–H hyperconjugative order. However, rate constants, heats of activation *and* entropies of activation are consistent with the viewpoint that inherent release by alkyl is in the inductive order and steric hindrance to solvation acts to invert the rate order.†[5] In the *meta*-alkyl series in the same solvent

* Rate constants for this reaction follow the inductive order in 56% acetone and the C–H hyperconjugative order in 85% ethanol.[15]

† Steric hindrance to solvation of electron-deficient sites in the substituted aromatic ring of the polar transition state would increase $\Delta H^{\ddagger}$ and this would act to decrease k. The same factor would increase $\Delta S^{\ddagger}$, by increasing the solvation entropy of the transition state, and this would tend to increase k. Presumably solvation effects on $\Delta H^{\ddagger}$ are more important in governing the k values.

[14] W. M. Schubert, J. M. Craven, H. Steadly and J. Robins, *J. Org. Chem.* **22**, 1285 (1957).
[15] E. Berliner, M. C. Beckett, E. Blommers and B. Newman, *J. Amer. Chem. Soc.* **74**, 4940 (1952).
[16] E. Berliner and L. C. Monack, *J. Amer. Chem. Soc.* **74**, 1574 (1952).
[17] E. D. Hughes, C. K. Ingold and N. A. Taher, *J. Chem. Soc.* 950 (1940).

a mild Baker–Nathan effect on the rate constants is observed (Table 6). Similar results are found in the solvolyses of *m*-alkylphenyldimethylcarbinyl chlorides in "90%" acetone at 25°.[19] Despite the small methyl-hydrogen rate constant spread, Berliner and H. C. Brown have attributed this result to "*meta*" C–H hyperconjugation being important enough to tend to give a C–H hyperconjugative order of release by the

TABLE 6. SOLVOLYSIS OF *m*-$RC_6H_4CHClC_6H_5$

R =	H	Me	Bu^t
"80%" *acetone*[18]			
$k \times 10^6$ sec^{-1} (0°)*	2·79	4·78	4·27
$\Delta H^{\ddagger}$	20·6	20·4	20·5
$\Delta S^{\ddagger}$	−8·9	−8·3	−8·2
"90%" *ethanol*[20]			
$k \times 10^6$ sec^{-1} (0°)	20·5	39·6	47·0

* The rate constants for ethyl and *iso*propyl are 4·28 and 3·93, respectively.[18]

alkyl groups. However, the rate results are equally consistent with the operation of mild steric hindrance to solvation of the substituted aromatic ring.* Unfortunately the $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ values are so close that no significance can be attached to their differences. The fact that the Baker–Nathan effect in the rate constants is weaker for the *meta*-alkyl than for the *para*-alkyl compounds would be difficult to rationalize in terms of steric hindrance to solvation of the direct reaction site (i.e., the central carbon atom),[6] but is consistent with steric hindrance to solvation *near* the alkyl group. In other words, steric hindrance to solvation of the electron-deficient ring of the transition state would be expected to be less of a factor in the *meta*-alkyl series than in the *para*-alkyl series, since in the *meta*-alkyl compounds the substituent is further removed from the sites of greatest electron deficiency in the ring. It is interesting to note that whereas the *meta*-methyl and *tert.*-butyl rates have the C–H hyperconjugative order in "80%" acetone, they are in the inductive order in "90%" ethanol (Table 6).[19] This shows that the Baker–Nathan effect on rate constants is solvent dependent, as pointed out by Shiner, who found that the effect of changing solvent upon the rate constants of the *meta*-alkyl compounds can be rationalized either in terms of steric hindrance to solvation and/or solvent enhancement of C–H hyperconjugation.[19]

A study has been made of the solvolysis of *meta*-dimethyl- and *meta*-di-*tert.*-butylbenzhydryl chlorides in "80%" acetone and "90%" ethanol. The expectation, in terms of steric hindrance to solvation, is that the second *tert.*-butyl group would considerably increase solvent shielding of electron-deficient sites in the substituted ring. This should result in a reduced activating effect by the second *tert.*-butyl group and an increase in both the heat and entropy of activation in proceeding from the dimethyl

* It is presumed that the positive charge in the substituted ring is distributed mainly to the *ortho* and *para* positions and that a bulky alkyl substituent in the *meta* position hinders ring solvation less than it does when attached to the *para* position.[5] Berliner and Chen have expressed a contrary opinion.[18]

[18] E. Berliner and M. M. Chen, *J. Amer. Chem. Soc.* **80**, 343 (1958).
[19] H. C. Brown, J. D. Brady, M. Grayson and W. H. Bonner, *J. Amer. Chem. Soc.* **79**, 1897 (1957).
[20] V. J. Shiner, Jr. and C. J. Verbanic, *J. Amer. Chem. Soc.* **79**, 371 (1957).

to the di-*tert.*-butyl compound. The results of Table 7 show that these expectations have been realized.

TABLE 7. SOLVOLYSES OF 3, 5-DIALKYLBENZHYDRYL CHLORIDES

R =	H	Me	Bu^t
"80%" *acetone:*			
$k \times 10^5$ sec^{-1} (0°)	0·279[18]	·955	·729
$k \times 10^5$ sec^{-1} (35°)	—	70·8	60·5
$\Delta H^{\ddagger}$	20·6[18]	20·0	20·5
$\Delta S^{\ddagger}$	−8·9[18]	−8·1	−6·6
"90%" *ethanol:*			
$k \times 10^5$ sec^{-1} (0°)	2·05[19]	7·32	7·60
$k \times 10^5$ sec^{-1} (35°)	—	483	523
$\Delta H^{\ddagger}$	—	19·4	19·7
$\Delta S^{\ddagger}$	—	−6·3	−5·3

Comparing firstly the solvolysis rate constants in "80%" acetone at 0° (Tables 6 and 7), it is seen that the second *tert.*-butyl group has less of an effect than the second methyl group in increasing the rate constant. The net result is that the Baker–Nathan effect in the rate constants is more pronounced for the dialkyl than for the mono-alkyl compounds, a result consistent with the premise that a second *tert.*-butyl group should enhance the shielding to solvation, of the substituted aromatic ring. Comparing heats of activation, it is seen that the heat of activation is significantly lowered by the introduction of a second methyl substituent, from 20·4 ± 0·1 kcal to 20·0 ± 0·1 kcal. Thus the second methyl substituent has the expected effect of further stabilizing the transition state relative to the ground state. By contrast, the introduction of a second *tert.*-butyl group did not decrease the heat of activation. In other words, the effect that the second *tert.*-butyl group should presumably exert in further stabilizing the transition state relative to the ground state, through electron release, is balanced by a factor tending to *decrease* stabilization of the transition state relative to the ground state. This factor could well be steric hindrance to solvation near the substituent. Also in agreement with this interpretation is the fact that the entropy of activation is significantly greater for the di-*tert.*-butyl than for the mono-*tert.*-butyl compound. Note also that both the heat and entropy of activation are greater for the di-*tert.*-butyl than the dimethyl compound.

In "90%" ethanol the results are qualitatively the same as in "80%" acetone, although the differences in kinetic parameters are smaller. As in "80%" acetone, the rate constant in "90%" ethanol is increased more by a second methyl than by a second *tert.*-butyl group. Also, both $\Delta H^{\ddagger}$ and $\Delta S^{\ddagger}$ are slightly greater for the di-*tert.*-butyl than for the dimethyl compound.

All the solvolysis results, then, find a consistent interpretation in terms of steric hindrance to solvation near the alkyl substituent. On the other hand, the changes in rate constants, heats of activation and entropies of activation brought about by the introduction of a second *meta*-methyl or *tert.*-butyl substituent are difficult to rationalize either in terms of the Baker–Nathan viewpoint or in terms of solvent enhancement of C–H hyperconjugation.

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SOME THOUGHTS ON THE BAKER–NATHAN ORDER*†

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Abstract—The present status of the Baker–Nathan order is discussed in terms of current interpretations. On the basis of the large amount of available experimental data, it is suggested that hyperconjugation of carbon–hydrogen bonds provides the most consistent and satisfactory explanation of this effect.

THE least controversial statement that can be made about the Baker–Nathan order[1] is that it is an experimentally observed order of reactivity, which places a series of alkylated benzene derivatives in a sequence which suggests electron release from the alkyl groups to be Me > Et > Pr^i > Bu^t, and therefore in a sequence opposite to that of the general inductive effect (Bu^t > Pr^i > Et > Me). This means that in a reaction which is favored by electron accession, a *p*-methyl compound will react faster than a *p-tert.*-butyl compound, while in a reaction involving a nucleophilic attack in the rate-determining step, a *p-tert.*-butyl compound will react faster than a *para*-methyl compound. The concept of the greater electron release of a methyl group than that of higher alkyl groups was originally postulated as an hypothesis in order to explain certain experimental facts,[1] and later became part of the hyperconjugation concept. The situation is similar today, except that, irrespective of explanation, a much larger and more consistent body of experimental data has accumulated, showing the Baker–Nathan phenomenon, than was the case over 20 years ago.

When the concept was postulated in 1935, there were actually very few cases known where clear-cut reactivity orders had been observed, orders that placed the four alkylated benzene derivatives in a monotonously changing sequence. Since then, many reactions have been examined where this is the case. However, one must recognize at the outset, and be resigned to it, that, in experiments with alkylated benzene derivatives, rate differences are usually extremely small and therefore the need for exact work is great. Nevertheless, many cases of clear-cut orders have been reported, in which the rate differences are beyond stated experimental errors and are experimentally reliable. Whether or not these small rate differences mean anything in terms of the problem of the relation of structure to reactivity is perhaps another question. For the present discussion this question is answered in the affirmative, because the consistency of the large body of data now available is sufficiently great and striking to justify an explanation. It is also true that, in spite of some very careful experimental work, activation energies and entropies rarely show sufficiently distinctive differences among the various compounds to be of help in interpreting the data, however much desirable a knowledge of these quantities would be, and by necessity,

* Electronic Effects of Alkyl Groups—X.

† Some of the ideas expressed here have been discussed in a previous publication. See E. Berliner and M. M. Chen, *J. Amer. Chem. Soc.* **80**, 343 (1958).

[1] J. W. Baker and W. S. Nathan, *J. Chem. Soc.* 1844 (1935); J. W. Baker, *Hyperconjugation*. Oxford University Press, Oxford (1952).

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one has to rely on rate differences. A justification of this has been given in other cases.[2, 3]

Even though accepted by most chemists, the concept of hyperconjugation as an explanation for the Baker–Nathan order has never been accepted by all. There are probably several reasons for this scepticism. One has perhaps arisen because in the valence bond description—in which the concept was first conceived—hyperconjugation or "no-bond" resonance structures constitute too much of a departure from views based on classical structural organic chemistry. Another reason is undoubtedly the very small experimental rate differences on which the concept is based (although rate differences showing the generally accepted inductive effect are usually not larger). Moreover, some reactions show either order of apparent electron release, depending on conditions, or no clear-cut order at all. And finally, the scepticism is not lessened by the ease with which practically every case of a Baker–Nathan order can be accounted for by other means.

It is therefore not surprising that instead of hyperconjugation other explanations have from time to time been suggested to account for the Baker–Nathan order.[4, 5, 6, 7] These alternate explanations usually endeavor to maintain the inductive effect (or the inductive order[5]) as the only,[6, 7] or the most important, mechanism (or order) by which alkyl groups release electrons, and ascribe the experimentally observed Baker–Nathan order to steric effects of one kind or other, which are assumed to reverse the normal inductive order and lead to the reactivity sequence Me > Bu^t. The present discussion will exclude those auxiliary concepts which have been added to modify the hyperconjugation explanation, but not to replace it, such as, for instance, steric inhibition of hyperconjugation due to lack of proper orbital overlap,[8] or solvent enhancement of hyperconjugation,[9] because these concepts implicitly acknowledge the operation of hyperconjugation effects. Also, various suggestions which have been made for single special cases, such as relief of steric strain in *meta*-alkyl groups,[10] or buttressing effects by *meta*-alkyl groups,[11] will not be considered. Unanswered will also remain the question if, on theoretical grounds, a methyl group, with three α-hydrogen atoms, should be more favorable to hyperconjugation than an ethyl group with only two but with one α-methyl group, and the latter more than a *tert.*-butyl group with no α-hydrogen atoms but with three α-carbon–carbon bonds. This notion, on which the original hypothesis was based, does not appear to have been worked out by the molecular orbital method, in which no distinction was made between hyperconjugation involving carbon–hydrogen or carbon–carbon bonds.[12] There are, however,

[2] C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Chapter 6. Cornell University Press, Ithaca, New York (1953).
[3] M. J. S. Dewar and R. J. Sampson, *J. Chem. Soc.* 2789 (1956).
[4] C. C. Price and D. C. Lincoln, *J. Amer. Chem. Soc.* **73**, 5836 (1951); C. C. Price and W. J. Belanger, *Ibid.* **76**, 2682 (1954).
[5] W. A. Sweeney and W. M. Schubert, *J. Amer. Chem. Soc.* **76**, 4625 (1954); W. M. Schubert and W. A. Sweeney, *J. Org. Chem.* **21**, 119 (1956); W. M. Schubert, J. Robins and J. L. Haun, *J. Amer. Chem. Soc.* **79**, 910 (1957); W. M. Schubert and J. Robins, *Ibid.* **80**, 559 (1958).
[6] A. Burawoy and E. Spinner, *J. Chem. Soc.* 3752 (1954).
[7] A. Burawoy and E. Spinner, *J. Chem. Soc.* 2085 (1955); E. Spinner, *Ibid.* 1590 (1956).
[8] G. Baddeley, J. Chadwick and S. B. Rawlinson, *Nature, Lond.* **164**, 833 (1949); G. Baddeley and M. Gordon, *J. Chem. Soc.* 2190 (1952); R. T. Arnold and W. L. Truett, *J. Amer. Chem. Soc.* **73**, 5508 (1951); V. J. Shiner, Jr., *Ibid.* **78**, 2653 (1956).
[9] V. J. Shiner, Jr., *J. Amer. Chem. Soc.* **76**, 1603 (1954); V. J. Shiner, Jr. and C. J. Verbanic, *Ibid.* **79**, 373 (1957).
[10] M. S. Newman and E. K. Easterbrook, *J. Amer. Chem. Soc.* **77**, 3763 (1955).
[11] R. A. Benkeser, R. A. Hickner and D. I. Hoke, *J. Amer. Chem. Soc.* **80**, 2279 (1958).
[12] R. S. Mulliken, C. A. Rieke and W. G. Brown, *J. Amer. Chem. Soc.* **63**, 41 (1941).

various indications, taken from rate and equilibrium data,[13] that a *tert.*-butyl group is capable of a resonance effect, in addition to its inductive effect, and that both carbon–hydrogen and carbon–carbon hyperconjugation play a role, but that the former is more important than the latter, and that their contributions might be in a constant ratio. Quantitative correlations between the structure of alkyl groups and their reactivities have been uncovered on this assumption.[14]

In earlier years certain cases of reactivity were ascribed to the Baker–Nathan effect, where it could easily be shown that the rate differences must actually be due to steric influences. For instance, substitution *ortho* to the methyl group by various electrophilic reagents in *p-tert.*-butyltoluene was ascribed to the greater electron releasing effect of the methyl group alone,[1] but an inspection of the partial rate factors for *ortho* substitution easily reveals that the orientation in these cases is predominantly influenced by the steric hindrance *ortho* to the large *tert.*-butyl group.[2] The more recent alternate explanations for the Baker–Nathan order which deserve the most serious consideration, because they are in themselves reasonable and have analogies in many reactions not pertaining to hyperconjugation, are those that ascribe the observed decrease in rate on going from a methyl to a *tert.*-butyl group to some sort of inhibition of solvation by the larger alkyl groups. One ascribes the decrease in rate on going from methyl to *tert.*-butyl to a "bulk effect" on solvent stabilization of a polar transition state, even by remote alkyl substituents which prevent solvent dipoles from proper orientation.[4] This explanation was used to account for the relative reactivities in the alkaline hydrolysis of ethyl *p*-alkylbenzoates in aqueous acetone, which follows an inductive order (i.e., a methyl compound reacts faster than a *tert.*-butyl compound because of a rate-determining nucleophilic attack) and, as expected for this effect, it was considered significant that the effect was greater for alkyl groups in the *meta* position, which is closer to the reaction site. A similar decrease in rate on increasing the size of substituents was also found in other ester hydrolyses, and the suggested explanation may well be of importance in these cases. (It is indicative of the perplexities one encounters on working with alkylated compounds—although not pertinent to the particular point under discussion—that the alkaline hydrolysis of the same ethyl *p*-alkylbenzoates in aqueous ethanol follows a hyperconjugation order.[15]) The other alternate explanation[5] postulates that the decrease in rate of a more highly branched alkylated benzene derivative is due to inhibition of solvation by alkyl groups of electron deficient centers, which develop in the transition state on the aromatic ring, at or near the alkyl groups, for instance in the solvolysis of *p*-alkylbenzhydryl halides.[16] This view was developed on the basis of the spectral behavior of alkylated compounds and various physical measurements on static molecules, where usually the inductive order is observed. Since a *tert.*-butyl group would have a greater "bulk effect" and also inhibit the solvation of the aromatic ring at, or near, the carbon atom to which it is attached more than the smaller methyl group, the observed reactivity order Me $>$ Bu^t can be accounted for.

[13] (a) E. Berliner and F. J. Bondhus, *J. Amer. Chem. Soc.* **70**, 854 (1948); P. D. Bartlett, *J. Chem. Educ.* **30**, 22 (1953); (b) C. A. Vernon, *J. Chem. Soc.* 423 (1954); (c) H. C. Brown, J. D. Brady, M. Grayson and W. H. Bonner, *J. Amer. Chem. Soc.* **79**, 1897 (1957).

[14] R. W. Taft, Jr. and I. C. Lewis, in press. I am indebted to Professor Taft for the personal communication prior to publication. See *Tetrahedron* **5**, 210 (1959).

[15] E. Berliner, M. C. Beckett, E. A. Blommers and B. Newman, *J. Amer. Chem. Soc.* **74**, 4940 (1952); C. W. L. Bevan, E. D. Hughes and C. K. Ingold, *Nature, Lond.* **171**, 301 (1953). However, see R. L. Herbst and M. E. Jacox, *J. Amer. Chem. Soc.* **74**, 3004 (1952).

[16] E. D. Hughes, C. K. Ingold and N. A. Taher, *J. Chem. Soc.* 949 (1940).

Either explanation is reasonable in itself, and these factors may be important. There is also no single clear-cut experiment by which these explanations can be shown to be either superior or inferior to that based on hyperconjugation. But while such steric factors may be important, it is the present contention that they do not satisfactorily account for all of the facts and are not decisive, and it is only when the large body of accumulated material is considered that a more consistent picture obtains on the hyperconjugation hypothesis. Such data are collected in Table 1. This table is not complete, nor is it meant to be. Some of the older literature data have been omitted, and only illustrative material has been collected which will fit into the three listed categories.

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On first sight one is impressed by the consistency of the data, which was not the case when the concept was first formulated. First of all, in all cases of electrophilic substitution in the *para* position for which exact data are available, a Baker–Nathan order is obtained. (Nos. 1–4). The only exception is nitration (No. 21), while rate constants for hydrogen–deuterium exchange in the *para* positions are the same within experimental errors.[17] A Baker–Nathan order is obtained for bromination by molecular bromine or by positive bromine, for benzoylation in nitrobenzene or in benzoyl chloride, as well as in the brominolysis and protonolysis of the trimethylsilyl group (Nos. 6 and 7). It is very likely also true for molecular chlorination,[18] for iodine-catalyzed bromination[19] and for mercuration,[20] although not all the necessary data are available for an exact comparison. It is also the case for various solvolytic reactions of the S_N1 or limiting case (Nos. 8–11), such as the solvolysis of benzyl halides, benzhydryl halides and cuminyl halides in various solvent mixtures, and for some S_N2 reactions on benzyl halides (Nos. 12–14), in which the spread in reactivity is less, as anticipated. Included are also solvolyses of acetylenic and allylic halides (Nos. 15 and 16) which, although not aromatic, constitute systems where an analogous behavior might be expected. Finally, some equilibrium constants which show the Baker–Nathan pattern are also listed (Nos. 19 and 20). It is therefore no longer true that the Baker–Nathan order is sometimes exhibited in electron demanding processes in aromatic systems, but it would be much more justified to say that the Baker–Nathan order is rarely not exhibited in such processes.

Because of the rate sequence *p*-Me > *p*-Bu^t, these are the reactions to which the alternate explanations apply. Two further observations are worth noting in this connection. One is that these reactions were conducted in a variety of solvents, but no systematic change in reactivity pattern is discernible. The other is that, while the ratio of methyl to *tert.*-butyl reactivities is not the same in the direct substitution reactions, these ratios are not due to a different behavior of the alkyl groups in the different reactions, but to the different susceptibility of each reaction to the electron demand of the substituting agents, i.e., to different rho values. This conclusion is based on the remarkably constant behavior of the methyl group in a great variety of substitution reactions, as shown by the excellent quantitative correlation of *para* and

[17] E. L. Mackor, P. J. Smit and J. H. Van Der Waals, *Trans. Faraday Soc.* **53**, 1309 (1957). This seems to be also true for *para* propylation. See F. E. Condon, *J. Amer. Chem. Soc.* **70**, 2265 (1948).
[18] P. B. D. de la Mare and P. W. Robertson, *J. Chem. Soc.* 279 (1943). According to a private communication from Dr. P. B. D. de la Mare, such data are now available, showing the Baker–Nathan order for *para* and the inductive order for *meta* chlorination. I am indebted to Dr. de la Mare for this information. See also *Tetrahedron* **5**, 107 (1959).
[19] E. Berliner and F. J. Bondhus, *J. Amer. Chem. Soc.* **68**, 2355 (1946); also in ref. 13.
[20] H. C. Brown and C. W. McGary, Jr., *J. Amer. Chem. Soc.* **77**, 2310 (1955).

TABLE 1A. SOME REACTIONS SHOWING THE BAKER–NATHAN ORDER OF ELECTRON RELEASE (Me > Bu^t)

Reference	Reaction No.		H	*p*-Me	*p*-Bu^t	*m*-Me	*m*-Bu^t
28	1	Bromination of benzenes by Br_2 (HAc)	1	2420	770	—	—
29	2	Benzoylation of benzenes (nitrobenzene)	1	830	615	—	—
21	3	Benzoylation of benzenes (benzoyl chloride)	1	589	430	—	—
30	4	Bromination of benzenes by (HOBr) (H^+) (50% aq. dioxan)	1	59	38·5	—	—
31	5	Chlorination of RO-2-Br-4-Alkyl-C_6H_3 by Cl_2 (HAc)	—	—	—	1·00	0·49
32	6	Brominolysis of $ArSiMe_3$ by Br_2 (HAc)	1	49	29	—	—
33	7	Protonolysis of $ArSiMe_3$ by $HClO_4$ (aq. methanol)	1	21·1	15·6	—	—
34	8	Solvolysis of $ArCH_2Br$ (wet HCOOH)	1	57·9	28·0	—	—
13c	9	Solvolysis of $ArCMe_2Cl$ (90% aq. acetone)	1	26·0	14·4	2·00	1·85
16, 23	10	Solvolysis of $Ar(C_6H_5)CHCl$ (80% aq. acetone)	1	21·4	10·9	1·68	1·53
35	11	Solvolysis of $Ar(C_6H_5)CHCl$ (90% aq. ethanol)	1	30·8	19·3	—	—
1	12	R. of $ArCH_2Br$ with C_5H_5N (acetone)	1	1·66	1·35	—	—
34	13	R. of $ArCH_2Br$ with I^- (acetone)	1	1·46	1·36	—	—
34	14	R. of $ArCH_2Cl$ with EtO^- (ethanol)	1	1·57	1·46	—	—
13b	15	Solvolysis of $RCH{=}CHCH_2Cl$ (wet HCOOH)*	1	3550	2260	—	—
6	16	Solvolysis of $RC{\equiv}CCMe_2Cl$ (80% aq. ethanol)*	1	2160	1180	—	—
36	17	Acid hydrolysis of Et_3SiOAr (aq. ethanol)	1	1·45	1·32	—	—
37	18	Beckmann rearrangement of $ArCOCH_3$ oximes (H_2SO_4)	1	1·86	1·78	—	—
38	19	Ionization of anilinium ions (24·6 wt. % aq. MeOH) pK_a	4·40	4·89	4·76	—	—
39	20	Ionization of 2-nitrophenols (24·5 wt. % aq. acetone) pK_a	7·57	7·89	7·76	—	—

* R in this reaction means H, Me or Bu^t.

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TABLE 1B. SOME REACTIONS SHOWING THE INDUCTIVE ORDER OF ELECTRON RELEASE (Bu^t > Me)

Reference	Reaction No.		H	*p*-Me	*p*-Bu^t	*m*-Me	*m*-Bu^t
40	21	Nitration of benzenes (HAc)	1	58	75	2·5	4·0
30	22	Bromination of benzenes by (HOBr) (H^+) (50% aq. dioxan)*	1	—	—	2·5	2·6
41	23	Iodination of *p*-alkylanilines (30% aq. methanol)	≃0·2	—	—	1·00	2·09
42	24	Iodination of *p*-alkylphenols (25% aq. methanol)	—	—	—	1·00	1·70
43	25	R. of pyridines with MeI (nitrobenzene)	1	—	—	2·07	2·77
11	26	Protonolysis of $ArSiMe_3$ (aq. HAc)	1	—	—	2·16	2·81
44	27	Decomposition of ArN_2^+ (0·1 N HCl)	—	—	—	1·00	3·60
35	28	Solvolysis of $Ar(C_6H_5)CHCl$ (90% aq. ethanol)	1	—	—	1·93	2·29
15	29	Alkaline hydrolysis of ethyl benzoates (56% aq. acetone)	1	0·41	0·31	—	—
4	30	Alkaline hydrolysis of ethyl benzoates (56% aq. acetone)	—	1	0·843	1·45	0·826
24	31	Ionization of $Ar(C_6H_5)_2CCl$ (liquid SO_2)	1	17·6	18·8	2·28	3·97
45	32	Ionization of pyridinium ions (H_2O) pK_a	5·17	—	—	5·68	5·82
46	33	Ionization of phenylacetic acids (H_2O) pK_a	4·31	4·37	4·42	—	—

* See ref. 18 for molecular chlorination.

TABLE 1C. SOME REACTIONS INVOLVING A NUCLEOPHILIC ATTACK AND SHOWING THE ORDER Me > Bu^t OF ELECTRON RELEASE

15	34	Alkaline hydrolysis of ethyl benzoates (85 wt. % ethanol)	1	0·44	0·56	—	—
10	35	Methanolysis of *l*-menthyl benzoates (methanol)	1	0·420	0·570	0·747	0·838
47	36	Neutral hydrolysis of benzoic anhydrides (75% aq. dioxan)	1	0·352	0·389	—	—
34	37	Ethanolysis of benzoyl chlorides (ethanol)	1	0·569	0·667	—	—
34	38	R. of N-benzylpyridinium ions with EtO^- (ethanol)	1	0·504	0·691	—	—
48	39	R. of 2-nitrobromobenzenes with piperidine (piperidine)	1	0·146	0·170	—	—
34	40	R. of 2, 6-dinitrochlorobenzenes with EtO^- (ethanol)	1	0·176	0·309	—	—

meta partial rate factors,[21] and on the good fit of the methyl and *tert.*-butyl groups in the $\rho\sigma^+$ relationship.[22] To put it differently, in reactions in which a large resonance effect of substituents is called for, the two alkyl groups behave just like many other substituents for which the linear free energy relationship holds.

There are some reactions, notably two solvolytic reactions (Nos. 9 and 10), where alkyl groups in the *meta* position also show the Baker–Nathan order. It has been reasoned elsewhere[23] that if this decrease, *m*-Me > *m*-Bu^t, were owing to solvation hindrance, a greater spacing between the two groups should be obtained, because they are closer to the reaction center. Actually, the spacing of the two groups is considerably closer than for the same two groups in the *para* position. A Baker–Nathan order from the *meta* position, however, is an exception, and it is of considerable importance that, in practically all cases of electrophilic substitution, *meta*-alkyl groups follow the inductive pattern, i.e., a *m-tert.*-butyl compound reacts faster than a *m*-methyl compound (Table 1B). This is eminently reasonable when the restriction is recalled that resonance effects are transmitted preferentially through the *ortho/para* positions, but as a rule not through the *meta* position, some exceptions not withstanding. The *meta*-alkyl groups therefore affect rates and equilibria mainly through their inductive effects.[24] It is difficult to see how the usually greater reactivity of the *m-tert.*-butyl than the *meta*-methyl compound can be accommodated with the solvation views, because the *meta*-alkyl groups are closer to the reaction sites, and also any solvation of the ring must be more inhibited by the larger alkyl group. This is what the alternate theories demand, yet in almost all cases the *m-tert.*-butyl compound reacts faster. On the solvation view, one could, of course, say that the *meta*-alkyl groups behave quite normally and their effects need no explanation; but that would not do, because specific solvent effects would be expected to have at least the same influence with *meta*- as with *para*-alkyl groups. Practically the only way to get around this difficulty (which does not arise if electronic effects are used as the explanation) is to postulate that, when alkyl groups are attached to the *meta* position, the demand for solvation of the transition state is less.

There is a third category of reactions which is well accounted for on the hyperconjugation hypothesis, but less so by steric factors. These are reactions which follow a Baker–Nathan order of electron release, but which, because of a nucleophilic rate-determining attack, result in the reactivity order H > Bu^t > Me (Table 1C). Here belong various basic hydrolyses of alkylbenzoates, aromatic nucleophilic displacements and some others. In these reactions, too, a *tert.*-butyl compound reacts faster than a methyl compound. Furthermore, the concept of steric resistance to bond contraction, advanced to account specifically for the Baker–Nathan order in reactions going through an electron-deficient transition state,[6, 7] does not seem to offer an explanation for these reactions.

The consistency of the data is persuasive and lends support to hyperconjugation as the explanation of the observed reactivities. With the various steric effects one cannot easily explain why a *tert.*-butyl compound should ever react faster than a methyl compound. These alternate suggestions can be maintained only if additional hypotheses are made about varying solvation demands, which essentially amounts to

[21] H. C. Brown and F. R. Jensen, *J. Amer. Chem. Soc.* **80**, 2296 (1958).
[22] H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.* **79**, 1913 (1957). See also ref. 21.
[23] E. Berliner and M. M. Chen, *J. Amer. Chem. Soc.* **80**, 343 (1958).
[24] See, for instance, N. N. Lichtin and P. D. Bartlett, *J. Amer. Chem. Soc.* **73**, 5530 (1951).

the new hypothesis that, in those reactions in which a *tert.*-butyl compound reacts faster than a methyl compound, rate decreasing solvation factors are not decisive, or that they are only decisive where a Baker–Nathan order is observed. It seems at the moment more satisfactory to account for the behavior of alkyl groups in terms of the two electronic effects, although it is very likely that solvation factors are also of some importance.

There are many things that are not yet fully explained by hyperconjugation as it pertains to the Baker–Nathan order and that need further investigation. Among these are the role of the solvent and solvation,[4, 5] solvation assistance,[9] the stereochemical requirements of hyperconjugation,[6] the significance of the secondary isotope effects,[9, 25] the relation between hyperconjugation and hydrogen participation,[26] the importance of carbon–carbon hyperconjugation,[13, 14] and probably others. The situation is admittedly complex, because alkyl groups affect rates by three different electronic mechanisms, carbon–hydrogen hyperconjugation, carbon–carbon hyperconjugation and the inductive effect, the last two of which reinforce each other. In addition, various solvation and specific solvent effects, as well as steric factors, must play some role. The difficulty is that one does not know quantitatively how important each of these factors is in determining the total behavior of an alkyl group, although encouraging attempts in this direction are being made.[27] In view of this complexity, it is surprising how consistent, on the whole, the over-all picture is, and there is therefore justification in the statement that the predominant effects of alkyl groups on the benzene ring are usually the hyperconjugation and the inductive effects.

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[25] V. J. Shiner, Jr., *J. Amer. Chem. Soc.* **75**, 2925 (1953); E. S. Lewis and C. E. Boozer, *Ibid.* **76**, 791 (1954); E. S. Lewis and G. M. Coppinger, *Ibid.* **76**, 4495 (1954); C. G Swain, T. E. C. Knee and A. J. Kresge, *Ibid.* **79**, 505 (1957); A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey and S. Suzuki *Ibid.* **80**, 2326 (1958).
[26] S. Winstein and J. Takahashi, *Tetrahedron* **2**, 316 (1958).
[27] M. M. Kreevoy and R. W. Taft, Jr., *J. Amer. Chem. Soc.* **77**, 5590 (1955); R. W. Taft, Jr., *Steric Effects in Organic Chemistry* (Ed. M. S. Newman) Chapter 13. Wiley, New York (1956). See also ref. 14.
[28] P. W. Robertson, P. B. D. de la Mare and B. E. Swedlund, *J. Chem. Soc.* 782 (1953); H. C. Brown and L. M. Stock, *J. Amer. Chem. Soc.* **79**, 1421 (1957).
[29] H. C. Brown, B. A. Bolto and F. R. Jensen, *J. Org. Chem.* **23**, 414 (1958).
[30] P. B. D. de la Mare and J. T. Harvey, *J. Chem. Soc.* 36 (1956); *Ibid.* 131 (1957).
[31] A. E. Bradfield and B. Jones, *Trans. Faraday Soc.* **37**, 726 (1941).
[32] C. Eaborn and D. E. Webster, *J. Chem. Soc.* 4449 (1957).
[33] C. Eaborn, *J. Chem. Soc.* 4858 (1956).
[34] C. W. L. Bevan, E. D. Hughes and C. K. Ingold, *Nature, Lond.* **171**, 301 (1953).
[35] V. J. Shiner, Jr. and C. J. Verbanic, *J. Amer. Chem. Soc.* **79**, 369 (1957).
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[37] D. E. Pearson, J. F. Baxter and J. C. Martin, *J. Org. Chem.* **17**, 1511 (1952).
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[40] H. Cohn, E. D. Hughes, M. H. Jones and M. A. Peeling, *Nature, Lond.* **169**, 291 (1952).
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[43] H. C. Brown, D. Gintis and L. Domash, *J. Amer. Chem. Soc.* **78**, 5387 (1956).
[44] E. S. Lewis and E. B. Miller, *J. Amer. Chem. Soc.* **75**, 429 (1953).
[45] H. C. Brown and X. R. Mihm, *J. Amer. Chem. Soc.* **77**, 1723 (1955).
[46] J. F. J. Dippy, *Chem. Rev.* **25**, 151 (1939).
[47] E. Berliner and L. H. Altschul, *J. Amer. Chem. Soc.* **74**, 4110 (1952).
[48] E. Berliner and L. C. Monack, *J. Amer. Chem. Soc.* **74**, 1574 (1952).

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EVALUATION OF RESONANCE EFFECTS ON REACTIVITY BY APPLICATION OF THE LINEAR INDUCTIVE ENERGY RELATIONSHIP–IV

HYPERCONJUGATION EFFECTS OF PARA-ALKYL GROUPS*

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Abstract—The σ^* (or σ_I) scale of inductive effects and the linear inductive energy relationship, inductive effect $= \sigma^* \rho^*$ (or $\sigma_I \rho_I$), enables an empirical but quantitative estimation of inductive effects on reaction rates and equilibria. In the present paper the inductive effects of *para*-alkyl groups (Me, Et, Pr^i, Bu^t) in diverse reactivities of benzene derivatives are evaluated in this manner by using the inductive reaction constants, ρ_I, obtained in previous work with groups such as NO_2, CN, OCH_3 and halogens.

The observed effects of the *para*-alkyl groups, i.e., log (k/k_0) values, upon correction for the inductive effects (equation (1)) give results (called R values) which are in accord with resonance theory. The Baker–Nathan order is obtained and the Berliner and the Bartlett theories of C–C hyperconjugation effects are confirmed. In most instances the R values follow satisfactorily Brown's empirical additive relationship (3): $R = n_H h_H + n_C h_C$, where n_H and n_C are the number of α–C–H and α–C–C bonds, respectively, in the alkyl group, and h_H and h_C are the corresponding hyperconjugation constants. The ratio h_H/h_C is found equal to $1{\cdot}3 \pm 0{\cdot}1$, totally independent (within these limits) of electron demand (ρ_I values range from -12 to $+6$), solvent, temperature and nature of the reaction process (rate or equilibrium). An independent method (equation (2)) of obtaining R values provides evidence of second-order solvation effects of alkyl groups in certain reactions.

The effects of alkyl groups on the transition energies of the O–O bands of the gaseous benzene ultraviolet spectra follow equation (3), providing independent evidence corroborating the above interpretation of R values.

The unequivocal evidence for C–C hyperconjugation in the aromatic reactivities has lead to a re-examination of the aliphatic series reactivities correlated previously by Kreevoy and Taft in terms of inductive and C–H hyperconjugation parameters. The R values obtained follow equation (3) with improved precision. However, $h_H/h_C = 2{\cdot}5$, in accord with the earlier conclusion that C–H hyperconjugation effects in these aliphatic series reactions are appreciably larger than C–C hyperconjugation effects.

EXTENSIVE evidence has been obtained for the concept of an approximately fixed quantitative order of inductive effects of substituent groups on reaction rates and equilibria.[1, 2, 3, 4, 5] Quantitative correlations of inductive effects by the relationship: inductive effect $= \sigma^* \rho^*$, have been made which are widely independent of reaction

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[1] G. E. K. Branch and M. Calvin, *The Theory of Organic Chemistry* pp. 193–200. Prentice-Hall, New York (1941).
[2] S. Winstein and E. Grunwald, *J. Amer. Chem. Soc.* **70**, 828 (1948).
[3] R. W. Taft, Jr., *J. Amer. Chem. Soc.* **74**, 3120 (1952); *Ibid.* **75**, 4231 (1953).
[4] R. W. Taft, Jr., *Steric Effects in Organic Chemistry* (Ed. M. S. Newman) Chap. 13. Wiley, New York (1956).
[5] R. W. Taft, Jr. and I. C. Lewis, *J. Amer. Chem. Soc.* **80**, 2436 (1958).

type.[3, 4, 5] Reaction series following this relationship and values of the reaction constant, ρ^*, are given in reference 4 (additional reactions subsequently reported may be found in references 7, 14, 15, 16, 17, 19 and 22). These correlations have been termed linear inductive (or polar) energy relationships.[4] The inductive substituent constants, σ^*, for R groups have been obtained by the method of Ingold[6] and of Taft[3] from rates of normal saponification and acid-catalyzed hydrolysis of esters, $RCO_2C_2H_5$, and from the ionization constants[1, 4] for carboxylic acids, RCO_2H (wherein $R = XCH_2$).

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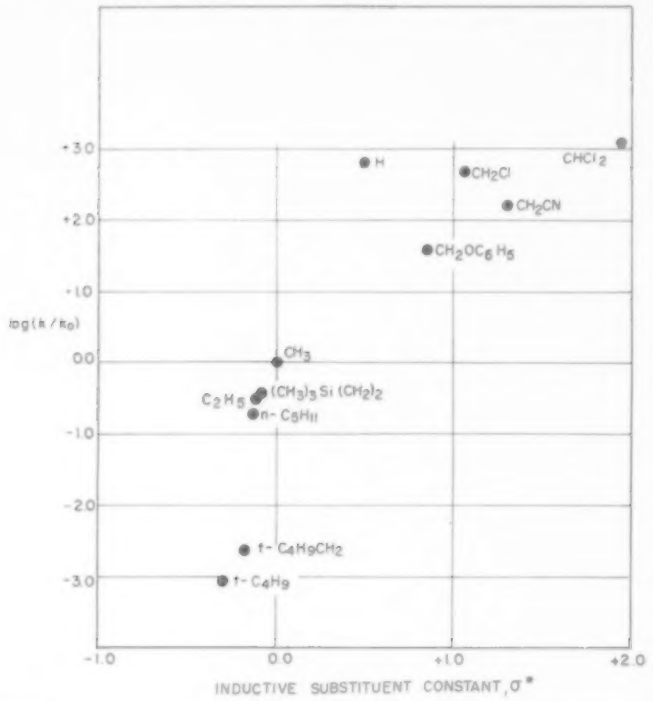

FIG. 1. Rates of sodium methoxide-catalyzed methanolysis of *l*-menthyl esters, $RCO_2C_{10}H_{19}$, in methanol at 30°.

Only when steric, resonance and other effects are very small (or negligible) in comparison to inductive effects do rates or equilibria for a reaction series follow the equation[3, 4]: $\log (k/k_0) = \sigma^* \rho^*$. In favorable cases, however, rates or equilibria which are complicated by steric effects may be corrected for these effects, and linear inductive energy relationships result. Figs. 1 and 2, taken from the work of Pavelich and Taft[7], provide an illustration of such a result.

Fig. 1 gives values of $\log (k/k_0)$ plotted vs. σ^* for the sodium methoxide catalyzed rates of methanolysis of a series of *l*-menthyl esters, $RCO_2C_{10}H_{19}$ (k_0 is the rate constant for the acetate ester). No direct relationship with σ^* values exists. In Fig. 2 the values of $\log (k/k_0)$ are corrected for steric effects, and, in contrast, a relatively precise

[6] C. K. Ingold, *J. Chem. Soc.* 1032 (1930).
[7] W. A. Pavelich and R. W. Taft, Jr., *J. Amer. Chem. Soc.* **79**, 4935 (1957); R. W. Taft, Jr. *Abstracts Fifteenth National Organic Chemistry Symposium* p. 53. Rochester, New York (June 1957).

correlation with σ^* values is obtained. The steric effect corrections are obtained by assuming a linear (steric energy) relationship[4, 8] between steric effects in the methanolysis rates and those in the rates of hydrolysis of corresponding esters.

A similar situation is found for rates or equilibria complicated by resonance effects.[4] An illustration is taken from the work of Taft and Lewis on application of the linear inductive energy relationship to the reactivities of *meta*- and *para*-substituted benzene derivatives.[5] In treating such reactivities it has proven convenient to "normalize"

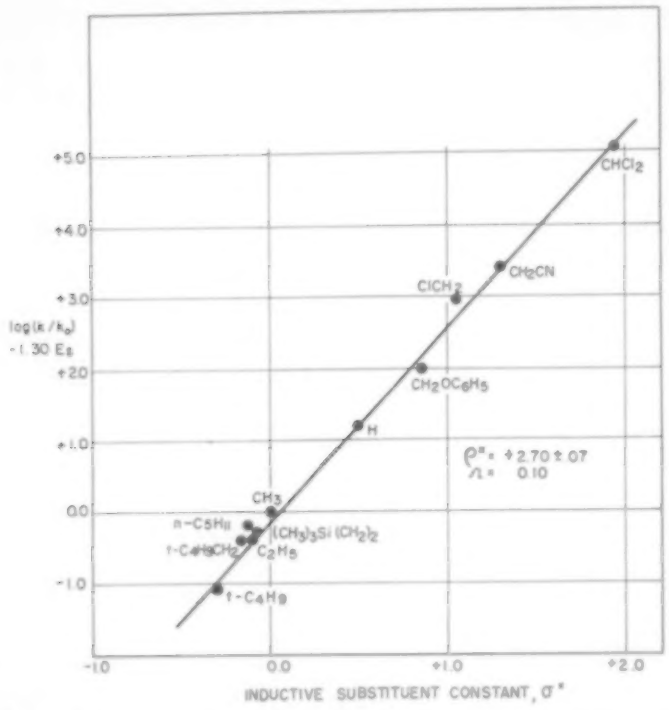

FIG. 2. Linear inductive energy relationship for rates of methanolysis of *l*-menthyl esters, R $CO_2C_{10}H_{19}$.

σ^* values so they are quantitative measures of the inductive contribution of Hammett's σ values.[9] It has been found that $0{\cdot}45\sigma^*_{XCH_2}$ gives the desired inductive constant for a *meta* or *para* substituent X relative to a hydrogen atom.[4] The inductive constants so obtained are given the symbol, σ_I.[10] Fig. 3 shows the wide scatter of points obtained in a plot of log (K/K_0) for the ionization of *meta*- and *para*-substituted benzoic acids in water at 25° vs. the inductive substituent constants, σ_I. This result is typical of the reactivities of *meta*- and *para*-substituted benzene derivatives in general.[5] Fig. 4 demonstrates the linear inductive energy relationship (inductive effect $= \sigma_I\rho_I$) which results upon correcting the log (K/K_0) values for resonance effects. This too is a

[5] R. W. Taft, Jr., *J. Amer. Chem. Soc.* **75**, 4538 (1953).
[9] L. P. Hammett, *Physical Organic Chemistry* p. 404. McGraw-Hill, New York (1940); references to earlier work are given in this book.
[10] R. W. Taft, Jr., *J. Amer. Chem. Soc.* **79**, 1045 (1957).

result typical of all types of aromatic reactivities involving uncharged *meta*- and *para*-substituents. The method used by Taft and Lewis to separate inductive and resonance effects of *meta*- and *para*-substituted derivatives of benzene is discussed at length in the later sections of this paper.

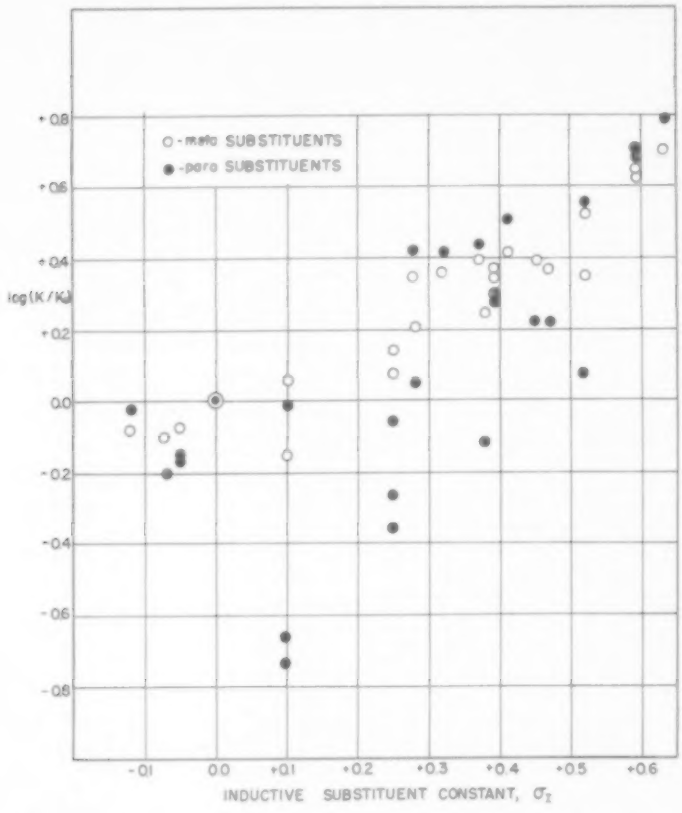

FIG. 3. Ionization of *meta*- and *para*-substituted benzoic acids in water at 25°.

A potentially valuable use which can be made of the linear inductive energy relationship is the approximately quantitative evaluation of the other effects (resonance, steric, etc.) of molecular structure on reactivity. This evaluation is obtained as the difference between the measured substituent effect and the calculated inductive effect.[4, 11] That is, $\log (k/k_0) - \sigma^* \rho^* =$ total effects other than inductive. In this way less ambiguous (perhaps in favorable cases unambiguous) studies of the other effects of molecular structure on reactivity are permitted via analysis of the relationship of these variables to structure. Interpretations reached on this basis may be further corroborated by additional generalized structure–reactivity relationships and by

[11] G. E. K. Branch and M. Calvin, *The Theory of Organic Chemistry* pp. 203–245. Prentice-Hall, New York (1951).

correlations with theoretical calculations.[12, 13] In this manner, studies of a quantitative nature have been made of intramolecular steric effects,[4, 7, 14] resonance effects[4, 5, 15, 16] and resonance energies,[12] anchimeric assistance,[17, 18, 19] the determination of fractional steric inhibition of resonance,[20, 21] and hydrogen bonding and steric effects on solvation.[22]

A major difficulty in the study of hyperconjugation effects* on reaction rates and equilibria has been the relatively small magnitude of effects which might be attributed

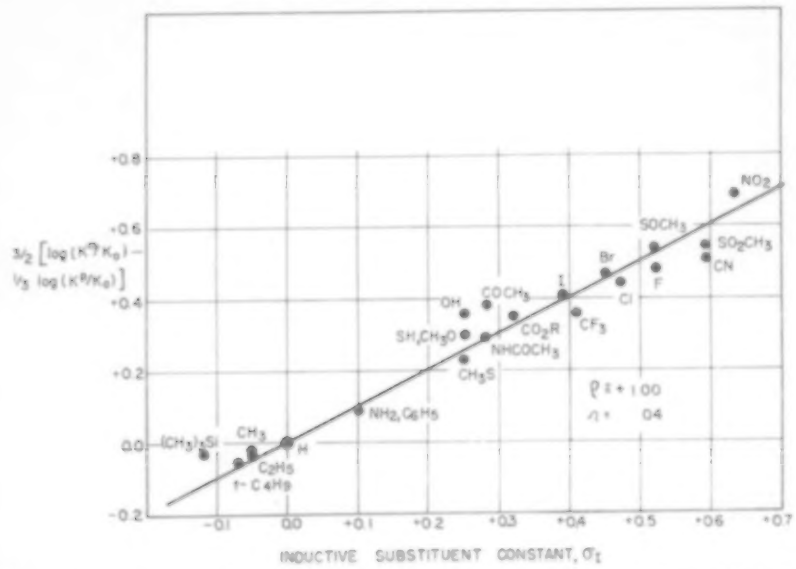

FIG. 4. Linear inductive energy relationship for the ionization of *meta*- and *para*-substituted benzoic acids.

to this cause and the attending uncertainty of their contribution to the measured reactivity relative to that of other effects, such as the inductive effect. As a result no body of characteristic observations of great generality has been forthcoming and the existence of direct hyperconjugation effects on reactivity has remained open to question.[23]

* The term hyperconjugation effect is used throughout the present paper in the general sense of denoting an effect on reactivity which results from a change during the reaction process in the total *potential energy of resonance interaction between an alkyl group and an adjacent atom with an open (unsaturated) stable orbital*—cf. further comments in the discussion section. The term hyperconjugation is not used as a connotation to distinguish between either of the two models which have been proposed to account for alkyl resonance interactions. Cf. references 13 and 61.

[12] M. M. Kreevoy and R. W. Taft, Jr., *J. Amer. Chem. Soc.* **79**, 4016 (1957).
[13] M. M. Kreevoy and H. Eyring, *J. Amer. Chem. Soc.* **79**, 5121 (1957).
[14] S. S. Biechler and R. W. Taft, Jr., *J. Amer. Chem. Soc.* **79**, 4927 (1957).
[15] M. M. Kreevoy and R. W. Taft, Jr., *J. Amer. Chem. Soc.* **77**, 5590 (1955).
[16] R. W. Taft, Jr. and M. M. Kreevoy, *J. Amer. Chem. Soc.* **79**, 4011 (1957).
[17] A. Streitwieser, Jr., *J. Amer. Chem. Soc.* **78**, 4935 (1956); *Chem. Rev.* **56**, 571 (1956).
[18] D. S. Noyce and B. R. Thomas, *J. Amer. Chem. Soc.* **79**, 755 (1957).
[19] S. Winstein, E. Alfred, R. Jeck and R. Glick, *J. Amer. Chem. Soc.* in preparation.
[20] B. M. Wepster, *Rec. Trav. Chim. Pays-Bas* **76**, 335, 357 (1957).
[21] R. W. Taft, Jr. and H. D. Evans, *J. Chem. Phys.* **27**, 1427 (1957).
[22] H. K. Hall, Jr., *J. Amer. Chem. Soc.* **79**, 5441, 5444 (1957).
[23] Cf., for example, W. A. Sweeney and W. M. Schubert, *J. Amer. Chem. Soc.* **76**, 4265 (1954).

The application of the linear inductive energy relationship to the quantitative estimation of the inductive contribution to widely diverse effects of alkyl groups on a variety of reactivities (in which hyperconjugation effects are expected in principle) leads to results which may be accounted for in terms of direct hyperconjugation effects.

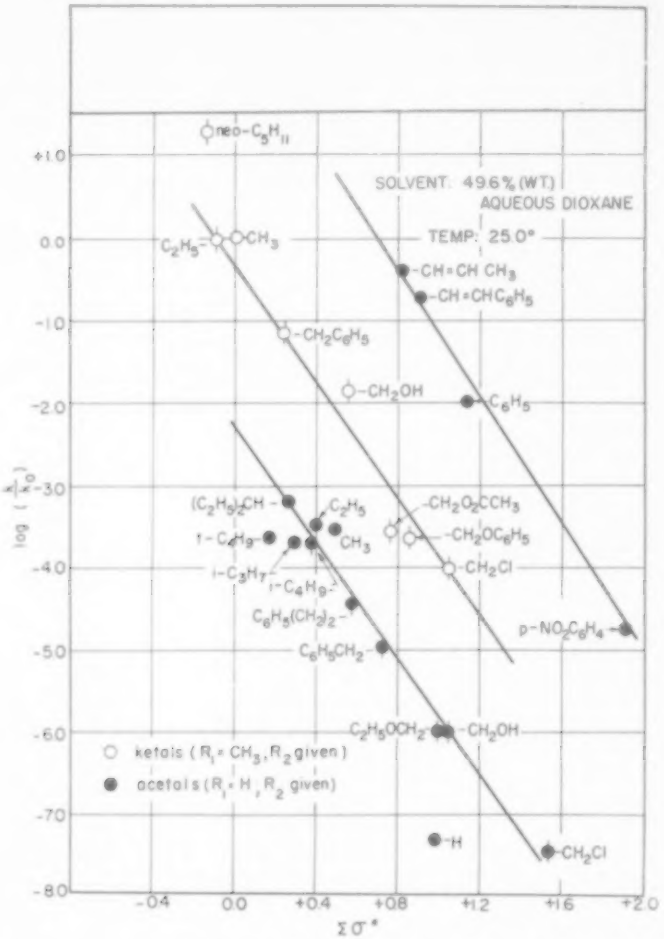

FIG. 5. Relationship between diethyl acetal and ketal, $R_1R_2C(OC_2H_5)_2$, hydrolysis rates and sum of polar substituent constants, σ^*, for R_1 and R_2.

Values of $\log (k/k_0) - \sigma^*\rho^*$ (or $\sigma_I\rho_I$) are related to alkyl structure in an approximately additive manner. Quantitative evidence is thereby provided that the measured reactivity effects are approximately the sum of inductive and hyperconjugation effects. The need to invoke more complex interpretations is frequently (but not always) lacking.

The method was first applied by Kreevoy and Taft[15] to the study of the effect of structure on the acid-catalyzed rates of hydrolysis of diethyl acetals and ketals,

$R_1R_2C(OC_2H_5)_2$, in 50 per cent aqueous dioxan at 25° with substituents of widely varying polar and steric requirements. A plot (Fig. 5) of log (k/k_0) vs. the sum of σ^* values of the substituents R_1 and R_2 leads to essentially parallel lines (slope $= \rho^* = -3{\cdot}60$) defined by the points for three classes: mono-substituted acetals, mono-substituted ketals (except methyl *tert.*-butyl and methyl *neo*pentyl ketals—cf. later discussion) and $\alpha\beta$-unsaturated acetals (with increasing intercepts in the order given). The conclusion was drawn that within each class, inductive electron release determines the increase in rate with variation of structure. The order of the increasing intercepts indicates that resonance stabilization of the oxo-carbonium ion-like transition state also contributes to increase the reaction rates. The rate constants for twenty acetals and ketals of unconjugated aldehydes or ketones (with the two exceptions indicated above) covering a spread of nearly eight powers of ten were fitted relatively satisfactorily by the equation:

$$\log (k/k_0) = (\Sigma\sigma^*)(-3{\cdot}60) + (0{\cdot}54)(n_H - 6)$$

wherein k_0 refers to acetonal and n_H to the total number of α-hydrogen atoms in R_1 and R_2. The constant 0·54 was attributed to the average stabilization of the reaction transition (in log units of rate) produced by an α-hydrogen atom Equations of this form were also found applicable to the correlation of the effects of unconjugated substituents on the gas-phase enthalpies of hydrogenation of mono- and *trans*-disubstituted ethylenes, and on the free energies of hydrogenation of carbonyl compounds, $R_1R_2C{=}O$, in toluene solution.[16] Steric effects are consequently implied to be nearly constant in each of these three reaction series.

In the present paper the results of the application of the linear inductive energy relationship to *para*(and *meta*)-alkyl groups in the reactivities of benzene derivatives are presented and considered in detail. These results, which are a part of the general evaluation of the resonance effects of *para* substituents by the method of Taft and Lewis,* provide evidence of both C–H and C–C hyperconjugation effects, and an approximately quantitative additive relationship of each to structure. A basis is also provided for modification of the earlier correlations of hyperconjugation effects in the aliphatic series.

PROCEDURE

The procedure of Taft and Lewis[5] is based upon the demonstration by Hammett and others[9] that the reactivities of *meta*- and *para*-substituted derivatives of benzene as a class are characterized as rarely if ever involving variable steric effects at the reaction center. The model equation used is: log (k^p/k_0) = inductive effect plus resonance effect. The further assumptions made are that (1) for unchanged substituents the inductive effect for all practical purposes is equivalent in the *meta* and *para* positions†

* Paper V, forthcoming *J. Amer. Chem. Soc.* This paper should be consulted for a discussion of the sense in in which the separation of log (k/k_0) values to I and R parameters is proposed. It is of particular importance to the present discussion to note that R values represent the total effect on reactivity other than that due to inductive delocalization of charge through the σ and π bonds (and space) between the alkyl group and the benzene ring (including any inductive effects arising as a consequence of the mesomeric inter-action). R values represent the total of the effects distinguished as resonance effect and resonance polar effect in ref. 4.

† For supporting evidence, cf. refs. 4 and 10 and J. D. Roberts, R. A. Clement and J. J. Drysdale, *J. Amer. Chem. Soc.* **73**, 2182 (1951), and J. D. Roberts and W. T. Moreland, Jr., *Ibid.* **75**, 2167 (1953).

while the resonance effect is reduced by a constant factor $\varkappa$ in the *meta* compared to the *para* position. That is:

$$\log (k^p/k_0) = I + R$$

$$\log (k^m/k_0) = I + \varkappa R,$$

where I is the inductive effect (called the I value) and R is the resonance effect (called the R value) from the *para* position.

Combining these equations to eliminate R:

$$I = \left[\frac{1}{1-\varkappa}\right] [\log (k^m/k_0) - \varkappa \log (k^p/k_0)]$$

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Using for the resonance effect fall-off factor, $\varkappa$, a value of 1/3 for those substituents which from the *para* position are conjugated only with the benzene ring and a value of 1/10 for those *para* substituents which undergo a change in conjugation with the first atom of the side-chain reaction center during the reaction process, I values have been obtained which follow the linear inductive energy relationship, $I = \sigma_I \rho_I$, for a wide variety of reaction types (Fig. 4 is an example). Included are reactivities which demand for correlation by the Hammett equation all of the proposed multiplicities of sigma values[9, 10, 24, 25] (σ, σ^-, σ^+), as well as some reactivities which do not satisfactorily fall into any of these schemes.[5]

The method leads to two independent (but equivalent, according to the model) means by which the resonance effects may be evaluated. First:

$$R = \log (k^p/k_0) - \sigma_I \rho_I \tag{1}$$

and second:

$$R = \left(\frac{1}{1-\varkappa}\right) \log (k^p/k^m) \tag{2}$$

To obtain the R value by equation (1) requires the knowledge of the rate or equilibrium constant for the *para* substituent relative to the unsubstituted derivative and the value* of the inductive reaction constant, ρ_I, based upon the inductive effects of substituents such as NO_2, CN, OCH_3, halogen, and others.[5] By equation (2), one must have the rate or equilibrium constant for the substituent in both the *meta* and *para* positions (the inductive effect is assumed to cancel in the ratio, k^p/k^m), and the appropriate value of the resonance fall-off factor, $\varkappa$ (cf. footnotes *m*, *n* and *o* of Table 2).

RESULTS AND DISCUSSION

R values for alkyl groups are potentially quantitative measures of the total hyperconjugation effects on rates and equilibria. This assignment can be substantiated by the demonstration of appropriate qualitative and quantitative relationships of R values to alkyl structure. For example, we may anticipate that these values will be

* For reactions which follow the Hammett equation, ρ_I values are the same as Hammett ρ values—cf. ref. 5.

[24] H. H. Jaffe, *Chem. Rev.* **53**, 253 (1953).
[25] H. C. Brown and Y. Okamoto, *J. Amer. Chem. Soc.* **79**, 1913 (1957); N. C. Deno and W. L. Evans *Ibid.* **79**, 5804 (1957).

positive for processes which are facilitated by electron release and negative for the contrary. Further, according to the classical Baker–Nathan effect,[26] we expect the magnitude of the R values to lie in the order Me > Et > Pr^i > Bu^t. Finally, according to the theoretically derived conclusions of Mulliken[61] and experimentally derived conclusions of Berliner,[27] the value for the Bu^t group should not be zero because of C–C hyperconjugation.

Of particular importance are quantitative relationships between R values and structure. Bartlett from a well-reasoned analysis (differing in rather minor detail from our method) of the effects of methyl and *tert.*-butyl groups on the free energy of ionization of *meta*- and *para*-substituted triphenylmethyl chlorides in liquid sulfur dioxide has obtained the estimate that the resonance effect of the *p*-methyl group is −1·18 kcal and the *tert.*-butyl group is −0·96 kcal.[28] Thus the C–H hyperconjugation effect exceeds that of C–C hyperconjugation by about 25 per cent. Bartlett concludes that, since the inductive effect of the *tert.*-butyl group is larger than that of the methyl group, the resultants of the three factors—the experimentally observed effects of the methyl and *tert.*-butyl groups on reactivity—are likely to appear confusing not only in this reaction, but generally.

More recently Brown *et al.*, by a method which also differs in minor detail from ours, have shown that the C–H and C–C hyperconjugation effects of *p*-methyl, *p*-ethyl, *p-iso*propyl and *p-tert.*-butyl groups in the rates of solvolysis of phenyldimethylcarbinyl chlorides in 90 per cent aqueous acetone, at 0–25°, are approximately additive.[29] Brown also finds for this reaction the same ratio of the C–H to C–C hyperconjugation effect as given above by Bartlett. That this figure should be the same for the two reactions under discussion is perhaps not surprising for both involve a similar change in inductive electron demand at the reaction center (ρ_I for both reactions is on the order of −4). We shall want to examine R values generally both with respect to the additive relationships and the dependence on reaction type (electron demand, solvent, etc.) of the ratio of the C–H to the C–C hyperconjugation effects.

Table 1 summarizes typical R values for a number of reaction series obtained by both equations (1) and (2). It is immediately apparent that each of the qualitative criteria of hyperconjugation effects mentioned above is satisfied by the R values. Attention may therefore be focused upon the quantitative aspects of the results. It may be seen from Tables 1 and 2 that equations (1) and (2), which according to our procedure should in principle give identical results, do not do so precisely. Generally, however, the agreement is considered quite satisfactory. The differences in several instances are probably due at least in part to ρ_I and to α values which have not been very precisely determined by the available data. In other instances the differences are probably quite real and this result will be discussed further.

The agreement between R values obtained by equations (1) and (2) for the reactions numbered 1, 2, 4, 7, 10 and 16 in Table 2 is probably representative of the order of precision that one can expect from the model equation and the method of quantitative separation of resonance and inductive effects. The average of the R values obtained

[26] J. W. Baker and W. S. Nathan, *J. Chem. Soc.* 1844 (1935).
[27] E. Berliner and F. J. Bondhus, *J. Amer. Chem. Soc.* **70**, 854 (1948).
[28] P. D. Bartlett, *J. Chem. Educ.* **30**, 29 (1953); N. N. Lichtin and P. D. Bartlett, *J. Amer. Chem. Soc.* **73**, 5530 (1951).
[29] H. C. Brown, J. D. Brady, M. Grayson and W. H. Bonner, *J. Amer. Chem. Soc.* **79**, 1897 (1957).

from the two equations for these reactions is also listed in Table 1. Finally Table 1 illustrates the quantitative additive relationship:

$$R = n_H h_H + n_C h_C \quad (3)$$

where n_H is the number of α-C–H bonds, n_C is the number of α-C–C bonds of the alkyl group, and h_H and h_C are C–H and C–C hyperconjugation constants, respectively (in log units of rate or equilibrium).

TABLE 1. R VALUES. CORRELATION BY EQUATION (3)*

Solvolysis of benzyhydryl chlorides, $Ar(C_6H_5)CHCl$

	7. 90% Aq. EtOH, 0° ($\rho_I \cong -4{\cdot}0$)				4. 80% Aq. acetone, 25° ($\rho_I \cong -4{\cdot}0$)			
	R(eqn. 1)	R(eqn. 2)	R(aver.)	R(calcd.) eqn. 3	R(eqn. 1)	R(eqn. 2)	R(aver.)	R(calcd.) eqn. 3
Me	+1·31	+1·33	+1·32	+1·32	+1·15	+1·22	+1·19	+1·20
Et	+1·22	—	+1·22	+1·22	+1·03	+1·19	+1·11	+1·10
Pr^i	+1·12	—	+1·12	+1·12	+0·89	+1·11	+1·00	+1·00
Bu^t	+1·00	+1·04	+1·02	+1·02	+0·75	+0·96	+0·86	+0·90
	$h_H = 0{\cdot}44$; $h_C = 0{\cdot}34$; $h_H/h_C = 1{\cdot}3$				$h_H = 0{\cdot}40$; $h_C = 0{\cdot}30$; $h_H/h_C = 1{\cdot}3$			

Solvolysis of *tert.*-cumyl chlorides, $Ar(CH_3)_2CCl$

	1. 90% Aq. acetone, 0° ($\rho_I \cong -4{\cdot}2$)				2. 90% Aq. acetone, 25° ($\rho_I \cong -4{\cdot}2$)			
	R(eqn. 1)	R(eqn. 2)	R(aver.)	R(calcd.) eqn. 3	R(eqn. 1)	R(eqn. 2)	R(aver.)	R(calcd.) eqn. 3
Me	+1·34	+1·34	+1·34	+1·35	+1·22	+1·23	+1·23	+1·23
Et	+1·22	+1·30	+1·26	+1·25	+1·11	+1·15	+1·13	+1·13
Pr^i	+1·09	+1·24	+1·17	+1·15	+1·00	+1·07	+1·04	+1·03
Bu^t	+0·95	+1·11	+1·03	+1·05	+0·86	+0·99	+0·93	+0·93
	$h_H = 0{\cdot}45$; $h_C = 0{\cdot}35$; $h_H/h_C = 1{\cdot}3$				$h_H = 0{\cdot}41$; $h_C = 0{\cdot}31$; $h_H/h_C = 1{\cdot}3$			

16. Ionization of pyridinium ions, $XC_5H_4NH^+$, H_2O, 25° ($\rho_I \cong +5{\cdot}7$)

	R(eqn. 1)	R(eqn. 2)	R(aver.)	R(calcd.) eqn. 3
Me	−0·59	−0·51	−0·55	−0·54
Et	−0·54	−0·48	−0·51	−0·49
Pr^i	−0·49	−0·45	−0·47	−0·44
Bu^t	−0·40	−0·26	−0·33	−0·39
	$h_H = -0{\cdot}18$; $h_C = -0{\cdot}13$; $h_H/h_C = 1{\cdot}4$			

* Numbers refer to the reaction series as listed in Table 2.

10. Bromination of benzene with HOBr, 50% Aq. dioxan, 25° ($\rho_I \cong -5{\cdot}8$)

	R(eqn. 1)	R(eqn. 2)	R(aver.)
Me	+1·50	+1·52	+1·51
Bu^t	+1·16	+1·31	+1·24

$h_H = +0{\cdot}50$; $h_C = +0{\cdot}41$; $h_H/h_C = 1{\cdot}2$

22. Methoxide-ion catalyzed methanolysis of *l*-menthyl benzoates, MeOH, 30°($\rho_I \cong +2{\cdot}6$)

	R(eqn. 1)	R(eqn. 2)	R(calcd.) eqn. 3
Me	−0·26	−0·37	−0·36
Et	−0·17	−0·32	−0·33
Pr^i	−0·12	−0·32	−0·30
Bu^t	−0·06	−0·26	−0·27

$h_H = -0{\cdot}12$; $h_C = -0{\cdot}09$; $h_H/h_C = 1{\cdot}3$

20. Decomposition of phenyldiazonium fluoroborates, ArN_2^+, H_2O, 47°($\rho_I \cong -3{\cdot}9$)

	R(eqn. 1)	R(eqn. 2)	R(calcd.) eqn. 3
Me	−1·15	−0·93	−1·17
Pr^i	−1·06	—	−1·05
Bu^s	−1·04	—	−1·05
Bu^t	−1·00	−1·08	−0·99

$h_H = -0{\cdot}39$; $h_C = -0{\cdot}33$; $h_H/h_C = 1{\cdot}2$

Table 2 summarizes the values of h_H, h_C and h_H/h_C obtained for all of the reactions for which the required data have come to our attention. The item of first importance in these results is the fact that $h_H/h_C = 1{\cdot}3 \pm 0{\cdot}1$, a figure which undoubtedly represents the relative conjugative capacities of C–H and C–C bonds in *para*-alkyl groups. This figure is quite independent of reaction type (it holds, for example, for equilibria between stable species as well as for reaction rates) and encompasses reactions with such variable changes in electron demand at the reaction center that ρ_I covers the enormous range from +6 to −12. Also without effect (within the indicated limits) on h_H/h_C are marked variations in solvent (from liquid C_6H_5COCl to aqueous H_2SO_4, for example) and temperature (0° to 51°). One must therefore look to considerable lengths if he is to avoid the conclusion that the *primary* effects of *para*-alkyl groups on these reactivities are caused by a change during the reaction process in the inductive and resonance potential energy interactions of the alkyl groups.

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TABLE 2. SUMMARY OF h_R AND h_C VALUES

Reaction	Eqn. (1)				Eqn. (2)			Reference
	h_R	h_C	h_R/h_C	ρ_I	h_R	h_C	h_R/h_C	
1. Solvolysis of $Ar(CH_3)_2CCl$, 90% aq. acetone, 0°	0·44[a]	0·33	1·3	−4·2[i]	0·45[a, m]	0·38	1·2	29
2. Solvolysis of $Ar(CH_3)_2CCl$, 90% aq. acetone, 25°	0·41[a]	0·29	1·4	−4·2[e]	0·41[a, m]	0·33	1·2	29
3. Solvolysis of $Ar(C_6H_5)CHCl$, 80% aq. acetone, 0°	0·43[a]	0·28	1·5	−4·0[j]	0·47[a, m]	0·37	1·3	30, 31
4. Solvolysis of $Ar(C_6H_5)CHCl$, 80% aq. acetone, 25°	0·38[a]	0·26	1·5	−4·0[j]	0·41[a, m]	0·32	1·3	30, 31
5. Solvolysis of $Ar(C_6H_5)CHCl$, 70% aq. acetone, 0°	0·44[a]	0·29	1·5	−4·0[j]	0·47[a, m]	0·37	1·3	32
6. Solvolysis of $Ar(C_6H_5)CHCl$, EtOH, 25°	0·40[a]	0·33	1·2	−4·0[j]	—	—	—	31
7. Solvolysis of $Ar(C_6H_5)CHCl$, 90% aq. EtOH, 0°	0·44[a]	0·34	1·3	−4·0[j]	0·45[a, m]	0·36	1·3	32
8. Ionization $Ar(C_6H_5)CHOH$, aq. H_2SO_4, 25°	0·48[a]	0·36	1·3	−5·6[g]	—	—	—	33
9. Ionization $Ar(C_6H_5)_2CCl$, liq. SO_2, 0°	0·37[d]	0·32	1·2	−3·7[g]	0·33[d, m]	0·25	1·3	34
10. Bromination of benzenes with HOBr, 50% dioxan, 25°	0·50[d]	0·39	1·3	−5·8[g]	0·51[d, m]	0·44	1·2	35
11. Bromination of benzenes with Br_2 in HOAc, 25°	0·91[e]	0·63	1·4	−12·1[g]	—	—	—	36
12. Benzoylation of benzenes in C_6H_5COCl, catalyzed by $AlCl_3$, 25°	0·78[d]	0·64	1·2	−9·6[g]	—	—	—	37
13. Benzoylation of benzenes in $C_6H_5NO_2$, with C_6H_5COCl, $AlCl_3$, 25°	0·82[a]	0·69	1·2	−10[g]	—	—	—	38
14. Brominolysis of $ArSi(CH_3)_3$, HOAc, 25°	0·48[a]	0·35	1·4	−5·7[e]	—	—	—	39
15. Protonolysis of $ArSi(CH_3)_3$, $HClO_4$ in 72% aq. MeOH, 51°	0·37[a]	0·29	1·3	−4·3[g]	—	—	—	40
16. Ionization of pyridinium ions, H_2O, 25°	−0·19[n]	−0·15	1·3	+5·7[e]	−0·17[n, o]	−0·12	1·4	41
17. Reaction of 2-nitrobromobenzenes with piperidine, 25°	−0·20[d]	−0·14	1·4	+5·0[h]	—	—	—	42

TABLE 2—*continued.*

Reaction	Eqn. (1)				Eqn. (2)			Reference
	h_R	h_C	h_R/h_C	ρ_I	h_R	h_C	h_R/h_C	
18. Reaction of 2-nitrobromobenzenes with piperdine, 35°	−0·20[d]	−0·13	1·5	+4·9[h]	—	—	—	42
19. Nitration of benzenes, Ac_2O, 45°	0·49[d]	0·46	1·1	−6·7[h, i]	+0·50[d, m]	+0·47	1·1	43
20. Decomposition of diazonium fluoroborates, H_2O, 47°	−0·39[d]	−0·33	1·2	−3·9[j, i]	−0·31[d, n]	−0·36	0·9	44
21. Ionization anilinium ions, H_2O, 25°	−0·12[e]	−0·07	1·7	+2·8[e]	−0·18[d, n]	−0·11	1·6	45
22. Methanolysis of *l*-$ArCO_2C_{10}H_{19}$, MeOH, 30°	−0·08[e]	−0·03	2·7	+2·6[e]	−0·12[e, b]	−0·09	1·3	46
23. Methanolysis of *l*-$ArCO_2C_{10}H_{19}$, MeOH, 40°	−0·06[e]	−0·02	3·0	+2·6[f]	−0·11[e, b]	−0·10	1·1	46
24. Saponification of $ArCO_2Et$, 85% aq. EtOH, 25°	−0·08[e]	−0·03	2·7	+2·3[e]	—	—	—	47
25. Hydrolysis of $(ArCO)_2O$, 75% aq. dioxan, 50°	−0·10[d]	−0·06	1·7	+3·3[f]	—	—	—	48
26. Hydrolysis of $(ArCO)_2O$, 75% aq. dioxan, 80°	−0·10[d]	−0·07	1·4	+1·8[f]	—	—	—	48
27. Ionization ArCOOH, H_2O, 25°	−0·04[e]	−0·04	1·0	+1·0[e]	−0·05[e, b]	−0·05	1·0	49
28. Alkaline hydrolysis Et_3SiOAr, 51% aq. EtOH, 25°	−0·05[d]	−0·04	1·3	+1·7[e]	—	—	—	50
29. Reaction of ArCHO with HCN, H_2O, 25°	−0·09[e]	−0·05	1·8	+0·9[f]	—	—	—	51

[a] Based on Me, Et, Pr^i, Bu^t.
[b] Based on Me, Pr^i, Bu^s, Bu^t.
[c] Based on Me, Et, Bu^t.
[d] Based on Me, Bu^t.
[e] ρ_I values given in ref. 5.
[f] ρ_I values determined from available data by method of ref. 5.
[g] Insufficient data available for determining ρ_I. Value given is ρ^+, obtained by the method of Brown and Okamoto, ref. 25 and unpublished results.
[h] Insufficient data available for determining ρ_I. Value given is ρ, H. H. Jaffe, *Chem. Rev.* **53**, 191 (1953). For a discussion of the validity of equating ρ and ρ_I values see ref. 5.
[i] ρ_I value for reaction 1 taken the same as for reaction 2.
[j] ρ_I value assumed to be approximately the same as for reaction 6.
[k] Value of ρ_I obtained from data at 25°.
[l] Based upon the ρ_I value for decomposition of diazonium chlorides, H_2O, 29°.
[m] Obtained by using $n = 1/10$.
[n] Obtained by using $n = 1/3$.
[o] Obtained by using $n = -0{\cdot}65$, based upon the decomposition of benzenediazonium chlorides—cf. ref. 5.

Apparent exceptions to the rule, $h_H/h_C = 1{\cdot}3 \pm 0{\cdot}1$, are to be found infrequently in Table 2 and where they do exist generally occur for reactions in which h_H is of smaller magnitude than $\pm 0{\cdot}10$. It is therefore probable that these apparent exceptions are not the result of any significant dependence of the hyperconjugation ratio, h_H/h_C, on reaction type, but rather result either from the lack of high precision of the method of separation of inductive and resonance effect, or the interference of small additional effects not considered in the model equation. In several reactions (notably reactions 20 and 22 of Tables 1 and 2, and reactions 5 and 23 of Table 2), equations (1) and (2) give sufficiently different R values to lead to discordant h_H/h_C ratios. With only a single notable exception (the R value for the CH_3 group in reaction 20), equation (2) in each instance gives results corresponding more closely to our general rule. It thus appears that log (k/k_0) values contain in these reactions an additional variable (or variables) other than inductive and hyperconjugative effects, whereas in values of $1/(1-\alpha)$ [log (k^p/k^m)] these variables (as well as the inductive effect) have essentially cancelled. The additional variables are probably to be associated with small but measureable specific alkyl solvation effects[32] (or possibly some other non-polar effects). It is possible that studies based upon the deviations of the results of equations (1) and (2) may be used to obtain a characterization of these secondary solvation (or other) effects.

The rates of decomposition of phenyldiazonium fluoroborates[44] (reaction 20) provide the exception noted above. While no explanation can be offered for the apparent anomalous R value for the methyl group obtained for this reaction by equation (2), it is important to note that this reaction is unique in that its rate is markedly *increased* by inductive electron-release ($\rho_I = -4{\cdot}2$) yet $-R$ *para* substituents (alkyl groups as in Table 1, or other such as OCH_3, Cl, etc.[5]) *retard* the rate. A reasonable explanation has been advanced by Bunnett and Zahler[52] and by Lewis[44] which accounts for the fact that resonance interaction of substituents of the latter class stabilize the reactant more than the transition state. This reaction therefore uniquely gives h and ρ_I values of the same sign.

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Sigma values

Reaction series which closely follow the Hammett equation,* $\log (k/k_0) = \sigma\rho$, give satisfactory linear relationships in plots of h_H or h_C values vs. ρ_I values. From the slopes of these plots, and the relationship[10] $R/\rho_I \equiv \sigma_R \equiv n_H h_H/\rho_I + n_C h_C/\rho_I$, one obtains the values of σ_R listed in Table 3. Included also in Table 3 are the values of σ_I and the Hammett σ values for *meta*- and *para*-alkyl groups which are consistent with the present general results. (The only σ value obtained in this manner which differs significantly from that obtained from the ionization of benzoic acid is the *p*-Bu^t value, given as −0·20 by the latter method[49]). The lack of a distinct ordering of the σ values for the alkyl groups is noteworthy and is in the line with Bartlett's earlier conclusion that composites of three contributing effects are not likely to bear distinct relationships to structure.[25] The inductive and C–C hyperconjugation effects generally lead to the same ordering of alkyl groups, i.e., Me < Et < Pr^i < Bu^t (the diazonium decomposition mentioned above is an exception), while the C–H hyperconjugation effects lead to the ordering Me > Et > Pr^i > Bu^t. Only the separation of σ values to these three contributing effects makes apparent the approximate additive relationships exhibited by each of these contributors.

The convincing feature of our results is that log (k/k_0) values for reaction series which show a distinct Baker–Nathan order, essentially no order (constant values for all alkyl groups), or as distinct "inductive" order all give essentially a fixed quantitative order of R values (i.e., R_{Me}: R_{Et} : R_{Pr^i} : R_{Bu^t} = 1·3 : 1·2 : 1·1 : 1·0). The cancellation of the order among inductive and hyperconjugation effects to give log (k/k_0) values which show no distinct order is apparently a common and sometimes confusing characteristic of alkyl groups.* This is illustrated by the constancy of the σ values for *para*-alkyl groups (Table 3) and by some further examples of log (k^p/k_0) values listed in Table 4. In the latter table, log (K^p/K_0) values for the diarylcarbinal–carbonium ion equilibria and for the pyridinium ion ionization equilibria conform to this pattern. By contrast, the log (k^p/k_0) values given for the benzhydryl chloride solvolysis in Table 4 show a distinct Baker–Nathan order, a result which becomes apparent for reaction series which have relatively large negative values for the ratio h_H/ρ_I.

TABLE 3. σ VALUES FOR ALKYL GROUPS

	σ_I	σ_R	σ_p	σ_m
Me	−0·046	−0·102	−0·15	−0·08
Et	−0·055	−0·094	−0·15	−0·09
Pr^i	−0·064	−0·086	−0·15	−0·09
Bu^t	−0·074	−0·078	−0·15	−0·10

The log (k^p/k_0) values for the decomposition rates of diazonium ions (also given in Table 4) provide a rare example in which the inductive and C–H hyperconjugation effects reinforce one another and are in opposition to the more minor C–C hyper-

* Cf. earlier discussion of this point by J. W. Baker, *Hyperconjugation* Chap. I. Oxford University Press (1952).

conjugation effect (h_H/ρ_I is positive), so that a distinct ordering of log (k/k_0) values is apparent.*

TABLE 4. EXAMPLES ILLUSTRATING CANCELLATION OF INDUCTIVE AND HYPERCONJUGATION EFFECTS IN LOG (k^p/k_0) VALUES FOR ALKYL GROUPS

Ionization $Ar(C_6H_5)CHOH$, aq. H_2SO_4, 25° ($\rho_I \cong -5{\cdot}6$; $h_H = 0{\cdot}48$)		Ionization pyridinium ions H_2O, 25° ($\rho_I \cong +5{\cdot}7$; $h_H = -0{\cdot}18$)	
	$\log(K^p/K_0)$		$\log(K^p/K_0)$
Me	+1·7	Me	−0·85
Et	+1·7	Et	−0·85
Pr^i	+1·7	Pr^i	−0·85
Bu^t	+1·5	Bu^t	−0·82
Solvolysis of $Ar(C_6H_5)CHCl$ 90% EtOH, 0° ($\rho_I \cong -4{\cdot}0$; $h_H = 0{\cdot}44$)		Decomposition of diazonium fluoroborates, H_2O, 47° ($\rho_I \cong -3{\cdot}9$, $h_H = -0{\cdot}39$)	
	$\log(k^p/k_0)$		$\log(k^p/k_0)$
Me	+1·34	Me	−0·97
Et	+1·27	Et	—
Pr^i	+1·17	Pr^i	−0·81
Bu^t	+1·05	Bu^t	−0·71

Similar plots of h_H and h_C values vs. ρ^+ values for the electrophilic reactions, for which H. C. Brown has proposed[25] the equation $\log(k/k_0) = \sigma^+\rho^+$, give less precise linear plots than those referred to above. While this result may be indicative of an inadequacy in Brown's relationship, it may equally well be due to uncertainties in available values of ρ^+ (these uncertainties fortunately do not produce very appreciable errors in obtaining R values for alkyl groups by equation (1)).

It is quite significant that the two equilibria of Table 4 conform to the $h_H/h_C = 1{\cdot}3$ rule (cf. Table 2) since the alkyl resonance is of the isovalent category in the aryl carbonium ions and of the sacrificial type in the pyridinium ion ionizations. Apparently then the relative hyperconjugation capacities of the C–H and C–C bonds are the same for Muller and Mulliken's two classifications of hyperconjugation.†

Finally it is important to note that the R values for reactions 16, 17, 18, 21 and 22 indicate that sacrificial hyperconjugation is not necessarily trivial in magnitude in ground states or transition states. This conclusion is strongly supported by shielding effects of m- and p-methyl substituents in the F^{19} fluorobenzene nuclear magnetic resonance spectra (cf. reference 10).

* Professor S. Winstein (in discussion) has pointed out that precise conformity to equations (1) and (3) demands that $\log(k^p/k_0)$ values for the series Me, Et, Pr^i and Bu^t must lie in a regular order (either increasing, decreasing or one in which the ordering is so slight that $\log(k/k_0)$ are essentially constant). Thus any reaction series for which $\log(k/k_0)$ values show an *inversion* among this series of alkyl groups does not conform precisely to these equations. Actually, all the reactions listed in Table 2 show a regular order of $\log(k^p/k_0)$ values, with the sole exception of reaction 27, which shows a very slight inversion order.

† N. Muller and R.S. Mulliken, *J. Amer. Chem. Soc.* **80**, 3489 (1958) cf. also R. S. Mulliken. this volume, p. 253.

Ultraviolet spectra of alkylbenzenes

Matsen and coworkers[53, 54] have made a thorough study of the effect of alkyl- and chlorine-substituted alkyl groups on the ultraviolet absorption spectra of benzene in the vapor phase. These spectra were determined under conditions of high resolution and detailed band assignments were made. Of particular interest are the positions of the so called O–O bands. This band is due to the transition between the zero point vibrational levels of the ground state and the first excited state. The position of this band provides the closest direct experimental measure of the difference in the electronic energies of the excited and the ground state. The position of the O–O bands of the alkylbenzenes generally differs quite appreciably from the position of the integrated maximum of all of the peaks for the 2600 Å ultraviolet bands.

There is much spectroscopic evidence that the transition from the ground to the first excited state of benzene is accompanied by enhanced resonance interaction of the substituent in the excited state but there is no appreciable inductive effect on the transition energy.[53–55] Matsen's data not only verify this conclusion qualitatively[53] but also quantitatively. The effects of open-chain alkyl substituents on the O–O-band transition energies follow equation (3) quite precisely, i.e., $\Delta\Delta\epsilon = n_H h_H + h_C h_C$ with $h_H = -0{\cdot}025$ eV, $h_C = -0{\cdot}018$ eV and $h_H/h_C = 1{\cdot}4$. The experimental values of $\Delta\Delta\epsilon$ and those correlated by this equation are listed in Table 5. This correlation of spectral data appears to afford strong confirmation of the conclusions concerning hyperconjugation reached from the analysis of reactivity effects.

The agreement between calculated and observed $\Delta\Delta\epsilon$ values (Table 5) for n-C_3H_7, $ClCH_2CH_2$ and $ClCH_2CH_2CH_2$ substituents shows that the values of h_H and h_C are not appreciably affected (although perhaps slightly*) by the inductive effect of replacing a β-CH_3 group by a β-CH_2Cl group or a β-Cl atom. The possible effect of mass of the substituent on the transition energies is also indicated as being of minor importance.[54]

Robertson *et al.*[56] also investigated the cyclic substituents: *cyclo*propyl, *cyclo*pentyl and *cyclo*hexyl. A very substantial red shift is observed for the O–O band for the *cyclo*propyl group ($\Delta\Delta\epsilon = -0{\cdot}152$ eV) in accord with much other evidence of the unsaturated nature of this group. The *cyclo*hexyl group gives the same transition energy as expected for a secondary open-chain alkyl group (cf. Table 5). The *cyclo*pentyl group, however, gives a red shift ($\Delta\Delta\epsilon = -0{\cdot}081$ eV) larger even than that for the methyl group. The authors assume that this results from a certain unsaturated character in the *cyclo*pentyl ring. The lack of general evidence of such unsaturated character, however, suggests the alternate possibility that the α-hydrogen atoms in the *cyclo*pentyl ring are held in a position especially favorable to hyperconjugative interaction.†

* For possible evidence of inductive effects on hyperconjugation which are in opposite direction to the slight apparent trend shown in Table 5. Cf. J. W. Baker, J. A. L. Brieux and D. G. Saunders, *J. Chem. Soc.* 404 (1956).

† Cf. in this connection the paper by W. R. Moore, Erich Marcus, S. E. Fenton and R. T. Arnold, p. 179 of this volume.

[53] F. A. Matsen, W. W. Robertson and R. L. Chuoke, *Chem. Rev.* **41**, 273 (1947).
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TABLE 5. CORRELATION BY EQUATION (3) OF THE TRANSITION ENERGIES FOR THE 0–0 BANDS OF THE GAS-PHASE ULTRAVIOLET ABSORPTION SPECTRA OF ALKYL BENZENES

Substituent	$\Delta\Delta\epsilon$ exptl. (eV)	$\Delta\Delta\epsilon$ calcd. eqn. (3) (eV)
*cyclo*Pentyl	−0·081	−0·061
CH_3	−0·076	−0·075
C_2H_5	−0·070	−0·068
$ClCH_2CH_2CH_2$	−0·069	−0·068
$ClCH_2CH_2$	−0·066	−0·068
Pr^i	−0·060	−0·061
Bu^s	−0·062	−0·061
*cyclo*Hexyl	−0·062	−0·061
Bu^t	−0·054	−0·054

In a further study Hamner and Matsen have determined the effects of CH_2Cl, $CHCl_2$ and CCl_3 groups on the O–O band transition energies.[54] Substantial red shifts are observed and these are attributed to hyperconjugation of the type:

We note that the observed transition energies follow approximately the equation: $\Delta\Delta\epsilon = n_H h_H + n_C{}^t h_C{}^t$, wherein the h_H value is that obtained above and the h_{Cl} hyperconjugation parameter (−0·056) is that obtained from the observed value of $\Delta\Delta\epsilon$ for the CCl_3 group. This correlation is summarized in Table 6.

TABLE 6. CORRELATION OF THE TRANSITION ENERGIES FOR THE 0–0 BANDS OF THE GAS-PHASE ULTRAVIOLET ABSORPTION SPECTRA OF CHLOROMETHYL-SUBSTITUTED BENZENES BY THE EQUATION: $\Delta\Delta\epsilon = n_H h_H + n_{Cl} h_{Cl}$

Substituent	$\Delta\Delta\epsilon$ exptl. (eV)	$\Delta\Delta\epsilon$ calcd. eqn. (4) (eV)
CH_3	−0·076	−0·075
$ClCH_2$	−0·121	−0·106
Cl_2CH	−0·133	−0·137
Cl_3C	−0·167	−0·168

The results of Brown[57] and of Schubert *et al.*[58] on the effects of *para*-alkyl groups on the ultraviolet absorption spectra of nitrobenzene differ appreciably from Matsen's results with benzene. A possible explanation may lie with the fact that the former spectra were not resolved to give the precise position of the O–O bands. Further, since the exact nature of the electronic transition is in question, the possibility exists that

[57] W. G. Brown and H. Reagan, *J. Amer. Chem. Soc.* **69**, 1032 (1947).
[58] W. M. Schubert, J. Robins and J. L. Haun, *J. Amer. Chem. Soc.* **79**, 930 (1957); W. M. Schubert and J. Robins, *Ibid.* **80**, 559 (1958).

inductive effects make important contributions to the observed spectral shifts. As noted in the reactivity section of this paper, an experimentally observed quantity which is the appropriate composite of inductive, C–H and C–C hyperconjugation effects will show little distinct order among alkyl groups. This is the observed result for the *p*-alkyl nitrobenzene spectra.

Hyperconjugation effects in the aliphatic series

The unequivocal quantitative evidence for C–C hyperconjugation effects in the reactivities of *para*-substituted derivatives of benzene prompts a re-examination of the aliphatic series reactivities which Kreevoy and Taft[15, 16] have previously considered to be satisfactorily correlated by inductive and C–H hyperconjugation effects.

The inductive effects in the acid-catalyzed rates of hydrolysis of acetals and ketals, $R_1R_2C(OC_2H_5)_2$, have been well demonstrated (cf. Fig. 5 and earlier discussion) to follow the linear inductive energy relationship: inductive effect $= (\Sigma\sigma^*)(-3{\cdot}60)$, and, with the probable exception of methyl *neo*pentyl and *tert.*-butyl ketals, steric effects have been shown to be nearly constant. Consequently, resonance effects (R values) may be obtained for this reaction by the relationship:

$$\log(k/k_0) - (\Sigma\sigma_H^*)(-3{\cdot}60) = R \qquad (5)$$

Column 2 of Table 7 lists R values so obtained from the $\log(k/k_0)$ values given in column 1.† The values listed are relative to the hydrogen atom as the standard of comparison, that is with k_0 corresponding to the rate constant for formal ($R_1 = R_2 =$ H) and σ^* values adjusted to H (instead of the methyl group) as the standard of comparison (designated accordingly as $\sigma_H)^*$.

With the exception of methyl *neo*pentyl and *tert.*-butyl ketals, R values for a variety of alkyl substituents follow quite precisely the relationship: $R = n_H h_H + n_C h_C$, with $h_H = 0{\cdot}62$ (log units), $h_C = 0{\cdot}24$ (log units) and $h_H/h_C = 2{\cdot}6$. This is demonstrated by the agreement between the values in columns 2 and 3 of Table 7. The latter column gives the R values calculated by this correlation. For comparison, values of R calculated by the earlier correlation, $R = (0{\cdot}54)n_H$, are shown in column 4. Both the evidence from the aromatic series reactivities and the improved precision of correlation of these R values appear to justify the C–C hyperconjugation terms for the acetal and ketal hydrolysis rates. The details of this modification in the interpretation of these reactivities are, however, in accord with the conclusion of Kreevoy and Taft that the principle conjugative effect for alkyl groups is a C–H hyperconjugation effect and the C–C hyperconjugation effect is by comparison sufficiently smaller to be approaching the limits of reliability of the method. Also unaffected is the earlier demonstration[12] that the acetal transition state is stabilized by conjugation with $\alpha\beta$-unsaturated substituents to an extent about one power of ten greater than that by hyperconjugation by an α-C–H bond (note that R values for the $\alpha\beta$-unsaturated groups listed at the bottom of Table 7 are on the order of $10\,h_H \cong 6$).

In one attributes the quantity, $\log(k/k_0) - (\Sigma\sigma_H^*)(-3{\cdot}60) - n_H h_H - n_C h_C$, to steric assistance to the hydrolysis rates for methyl *neo*pentyl and *tert.*-butyl ketals, driving forces amounting to $+1{\cdot}0$ and $+2{\cdot}0$ log units, respectively, are obtained.

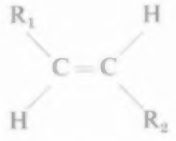
† Since the value of ρ^* is for all practical purposes determined by the substituents, R = $ClCH_2$, $BrCH_2$, $ROCH_2$ and $C_6H_5CH_2$, the R values of Table 7 may be regarded as based upon independently determined inductive effects.

TABLE 7. *R* VALUES FOR THE RATES OF HYDROLYSIS OF ACETAL AND KETALS $R_1R_1C(OEt)_2$, 50% DIOXON–WATER, 25°

Substituents				Column 1	Column 2	Column 3	Column 4
R_1	R_2	n_H	n_C	$\log(k/k_0)$	*R* eqn. (5) (log units)	*R* calcd. eqn. (3)	$n_H(0{\cdot}54)$
H	H	0	0	0·0	0·0	0·0	0·0
H	Bu^t	0	3	+3·7	+0·7	+0·7	0·0
H	Pr^i	1	2	+3·6	+1·1	+1·1	+0·5
H	$(C_2H_5)_2CH$	1	2	+3·9	+1·3	+1·1	+0·5
H	C_2H_5	2	1	+3·8	+1·6	+1·4	+1·1
H	Bu^t	2	1	+3·6	+1·4	+1·4	+1·1
H	$CH_2CH_2C_6H_5$	2	1	+2·8	+1·4	+1·4	+1·1
H	CH_3	3	0	+3·8	+2·0	+1·9	+1·6
CH_3	C_2H_5	5	1	+7·2	+3·4	+3·3	+2·7
CH_3	CH_3	6	0	+7·3	+3·7	+3·7	+3·2
H	$CH_3CH=CH$	—	—	+6·9	+5·2	—	—
H	$C_6H_5CH=CH$	—	—	+6·6	+5·1	—	—
H	C_6H_5	—	—	+5·2	+5·0	—	—
H	p-$NO_2C_6H_4$	—	—	+2·6	+5·0	—	—

These figures are in reasonable accord with estimates by Streitwieser[17] for steric assistance driving forces in the solvolysis rates for similarly crowded tertiary carbinyl halides.

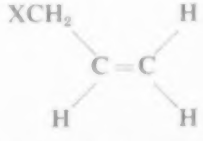
Table 8 gives the results of a similar re-examination of the effects of substituents on the enthalpies of hydrogenation of *trans*-disubstituted ethylenes



in the vapor phase at 355°K. *R* values are obtained from the relationship:

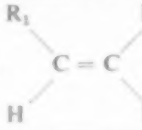
$$R = \Delta H_0 - \Delta H_0^0 - (-2{\cdot}2)(\Sigma\sigma_H^*) \qquad (6)$$

The value of $\rho^* = -2{\cdot}2 \pm 0{\cdot}2$ is based upon the linear inductive energy relationship obtained with olefins of the general formula



which is illustrated in Table 9. Because of the much more limited range of polarities covered by the available data, this ρ^* value cannot be as confidently accepted as that for the acetal and ketal hydrolysis. Taft and Kreevoy[16] maintain that a decrease in enthalpy of hydrogenation with an increase in electron-withdrawing power of the

substituent is expected because of the greater electronegativity of the unsaturated (sp^2) than the saturated (sp^3) central carbon atoms.

TABLE 8. R VALUES FOR THE ENTHALPIES OF HYDROGENATION OF TRANS-DISUBSTITUTED ETHYLENES,  ; GAS PHASE, 355°K

Substituents				Column 1	Column 2	Column 3	Column 4
R_1	R_2	n_H	n_C	$\Delta\Delta H°$ (kcal)	R eqn. (6) (kcal)	R calcd. eqn. (3)	$n_H(0{\cdot}44)$
H	H	0	0	0·0	0·0	0·0	0·0
H	Bu^t	0	3	+2·5	+0·7	+0·6	0·0
H	Bu^s	1	2	+2·4	+0·8	+0·9	+0·4
H	Pr^i	1	2	+2·5	+0·9	+0·9	+0·4
H	Et	2	1	+2·5	+1·2	+1·2	+0·9
H	Pr^n	2	1	+2·6	+1·2	+1·2	+0·9
H	Bu^i	2	1	+2·7	+1·3	+1·2	+0·9
H	Pe^{neo}	2	1	+3·3	+1·8	+1·2	+0·9
H	$CH_2CH_2CO_2R$	2	1	+1·7	+1·1	+1·2	+0·9
H	$CH_2CH=CH_2$	2	1	+2·2	+1·4	+1·2	+0·9
H	Me	3	0	+2·7	+1·6	+1·5	+1·3
Bu^t	Bu^t	0	6	+4·9*	+1·0	+1·2	0·0
Me	Bu^t	3	3	+4·5*	+2·0	+2·1	+1·3
Me	Pr^i	4	2	+5·0	+2·3	+2·4	+1·8
Et	Et	4	2	+5·2	+2·5	+2·4	+1·8
Me	Et	5	1	+5·2	+2·8	+2·7	+2·2
Me	Pr^n	5	1	+5·2	+2·8	+2·7	+2·2
Me	CH_2CO_2R	5	1	+3·2	+2·5	+2·7	+2·2
Me	Me	6	0	+5·2	+3·0	+3·0	+2·6
H	C_6H_5	—	—	+4·2	+4·4	—	—
H	$CH=CH_2$	—	—	+6·0	+5·7	—	—

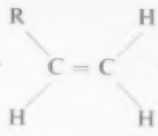
Column 2 of Table 8 lists R values for the olefin hydrogenation obtained as indicated above (equation (6)). Column 1 gives the experimental values of the enthalpies of hydrogenation relative to ethylene. Column 3 of this Table lists values of R as correlated by the equation:

$$R = n_H h_H + n_C h_C \qquad (3)$$

with $h_H = +0{\cdot}50$ kcal, $h_C = +0{\cdot}20$ kcal and $h_H/h_C = 2{\cdot}5$. Column 4 lists R values as calculated by the earlier correlation equation: $R = (0{\cdot}44)n_H$. Again the improved precision of the correlation equation which includes the C–C hyperconjugation term is distinctly noticeable. The mean deviation from equation (3) is of the order of experimental uncertainty (the deviation for the *neo*pentyl group suggests a steric effect).

* Obtained from the data of R. B. Turner, D. E. Nettleton, Jr. and M. Perelman, *J. Amer. Chem. Soc.* **80**, 1430 (1958), assuming the same value of $\Delta\Delta H$ for acetic acid solution and the vapor phase.

TABLE 9. DETERMINATION OF ρ^* FOR THE HYDROGENATION OF SUBSTITUTED ETHYLENES, GAS PHASE, 355°K

Based upon $\Delta\Delta H^\circ = -2{\cdot}2\,(\Delta\sigma^*)$ for  with R = CH_2X

X	$\Delta\Delta H^\circ$ obs. (kcal)	$\Delta\Delta H^\circ$ calcd. (kcal)
OH	−1·2	−1·4
CH_2CO_2R	−0·8	−0·8
$CH=CH_2$	−0·3	−0·5
$CH_2CH=CH_2$	0·0	−0·3
Me	(0·0)	(0·0)
Et	+0·1	+0·1
Pr^i	+0·2	+0·1
		aver. dev. = ±0·1

The fact that equation (3) is precisely followed for R groups of widely varying steric requirements (for example, $R_1=R_2=H$ to $R_1=R_2=Bu^t$) provides evidence of a constancy of steric effects, implying that the effect of σ bond expansion on the change between the sp^2 and sp^3 valence states[59] produces a contribution to the enthalpy of hydrogenation which is constant (with the possible exception of the *neo*pentyl group) for the compounds of Table 8. Deviations of *cis* and vicinally substituted ethylenes from equation (3), which may reasonably be associated with steric effects,[16] follow closely the empirical rules of Dewar and Pettit[60] dealing with the effects of such substitution on the enthalpies of hydrogenation.

Both Tables 7 and 8 provide examples which indicate that h_H and h_C are not appreciably affected by the inductive effects of polar substituents within the alkyl group. The approximate "10 to 1" rule of Kreevoy and Taft[12] for conjugative stabilization relative to C–H hyperconjugative stabilization of the olefin is illustrated by R values for two typical $\alpha\beta$-unsaturated substituents listed at the bottom of Table 8.

The free energies of hydrogenation of unconjugated carbonyl compounds, $R_1R_2C=O$, in dilute toluene solutions at 333°K are also correlated with slightly improved precision by the equation, $\Delta F^\circ - \Delta F_0^\circ = (-6{\cdot}0 \pm 0{\cdot}5)(\Sigma\sigma_H^*) + n_H h_H + n_H h_C$ (the standard of comparison is $R_1 = R_2 = H$, for which ΔF_0^0 is taken as 4·4 kcal more negative than that for acetaldehyde—the same as the difference between acetaldehyde and acetone). However, the data for this reaction are less accurate than the former two, and the ρ^* value has a substantial uncertainty. Consequently, a precise h_H/h_C value for this reaction is in question, but is probably also on the order of $2(h_H \cong 0{\cdot}5 \pm 0{\cdot}1$ kcal and $h_C \cong 0{\cdot}25 \pm 0{\cdot}1$ kcal). The uniquely systematic relationship of the extra resonance energies of conjugation and of hyperconjugation in carbonyl compounds and olefins found and discussed by Kreevoy and Taft[12] is

[59] M. J. S. Dewar and H. N. Schmeising, This volume, p. 166.
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Substituents				Column 1	Column 2	Column 3	Column 4
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H	H	0	0	0·0	0·0	0·0	0·0
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H	$CH_2CH=CH_2$	2	1	+2·2	+1·4	+1·2	+0·9
H	Me	3	0	+2·7	+1·6	+1·5	+1·3
Bu^t	Bu^t	0	6	+4·9*	+1·0	+1·2	0·0
Me	Bu^t	3	3	+4·5*	+2·0	+2·1	+1·3
Me	Pr^i	4	2	+5·0	+2·3	+2·4	+1·8
Et	Et	4	2	+5·2	+2·5	+2·4	+1·8
Me	Et	5	1	+5·2	+2·8	+2·7	+2·2
Me	Pr^n	5	1	+5·2	+2·8	+2·7	+2·2
Me	CH_2CO_2R	5	1	+3·2	+2·5	+2·7	+2·2
Me	Me	6	0	+5·2	+3·0	+3·0	+2·6
H	C_6H_5	—	—	+4·2	+4·4	—	—
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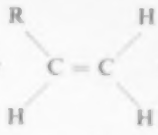
Based upon $\Delta\Delta H^\circ = -2{\cdot}2\,(\Delta\sigma^*)$ for  with R = CH_2X

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Pr^i	+0·2	+0·1
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Both Tables 7 and 8 provide examples which indicate that h_H and h_C are not appreciably affected by the inductive effects of polar substituents within the alkyl group. The approximate "10 to 1" rule of Kreevoy and Taft[12] for conjugative stabilization relative to C–H hyperconjugative stabilization of the olefin is illustrated by R values for two typical $\alpha\beta$-unsaturated substituents listed at the bottom of Table 8.

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[60] M. J. S. Dewar and R. Pettit, *J. Chem. Soc.* 1625 (1954).

essentially unaffected by this modification of including small C–C hyperconjugation effects.

Our interpretation of the enthalpies of hydrogenation of olefins and carbonyl compounds does not support the conclusion of Dewar and Schmeising[59] that resonance stabilization is of no importance in molecules such as butadiene or propene. Instead the relationships of R values to structure are those expected by resonance theory.[12] On the other hand, the possibility that effects associated with σ bond expansion make measureable contributions to these R values cannot be excluded.

The re-examination of these aliphatic series reactivities leads us to conclude that h_H/h_C is on the order of 2 to 3. The dependence of this value on electron demand is less certain than the demonstration of a constant h_H/h_C ratio for the aromatic series reactivities. However, ρ^* values (in log units) vary from -4 to $+4$ for the three reaction series with no indication of a pronounced change in h_H/h_C. The question of why h_H/h_C is materially larger for the aliphatic than the aromatic reactivities is one of interest and importance, but one for which we can give no satisfactory answer at present.

The Kreevoy and Eyring model[13, 61] for hyperconjugation (called α-hydrogen bonding by these authors) is attractive in accounting for the additive relationship (3). According to the naive model, Kreevoy and Eyring concluded that h_H/h_C should be of the order of 2 to 3. However, it is quite conceivable that h_H/h_C depends upon the unsaturated system to which the alkyl group is bonded. Thus the h_H/h_C ratio of 1·3 which holds so generally for the aromatic series reactivities may be associated with the common unsaturated system (phenyl) to which these alkyl groups are bonded. So few examples are available that it is by no means certain that h_H/h_C is a constant for aliphatic series reactivities. Definite answers to these questions awaits further experimental and theoretical investigations.

Acknowledgements—It is a pleasure to acknowledge correspondence with Dr. J. W. Baker concerning the subject of this paper. Helpful discussions with Professor R. S. Mulliken and Professor Lionel Goodman are also gratefully acknowledged.

[61] Compare with the classical model: R. S. Mulliken, C. A. Rieke and W. G. Brown, *J. Amer. Chem. Soc.* **63**, 41 (1941).

Tetrahedron, 1959, Vol. 5, pp. 233–242. Pergamon Press Ltd. Printed in Great Britain.

EXPERIMENTAL AND THEORETICAL EVALUATIONS OF THE BAKER–NATHAN EFFECT

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FOR a number of reactions in which steric effects can be neglected and relative reactivity can be sorted out into inductive and resonance contributions equations (1) hold with reasonable precision[1, 2, 3] In equations (1) $\rho^*\Sigma\sigma^*$ represents an

$$\log(k/k_0) = \rho^*\Sigma\sigma^* + B - (\Delta F_\psi/2{\cdot}3RT)$$
$$\Delta F - \Delta F_0 = \rho^*\Sigma\sigma^* + B + \Delta F_\psi$$
$$\Delta H - \Delta H_0 = \rho^*\Sigma\sigma^* + B + \Delta H_\psi \qquad (1)$$

inductive effect on reactivity.[4] The effect of conjugation on reactivity is given by ΔF_ψ or ΔH_ψ, which can be calculated with reasonable accuracy by the LCAO–MO method.[3, 5] B represents the Baker–Nathan effect.[6, 7] In previous work[1, 2, 3] the Baker–Nathan effect has been defined by equation (2), in which n is the number of

$$B = h(n - n_0) \qquad (2)$$

α hydrogens in a given compound, n_0 is the number in a standard compound and h is an empirically determined constant. Equation (2) suggests that the Baker–Nathan effect is peculiar to hydrogen atoms. A possible alternative to equation (2) is equation (3), in which the same Baker–Nathan effect is attributed to all alkyl groups. In equation (3), n' is the number of alkyl groups directly attached to a functional group, n_0' is the

$$B = h'(n' - n_0') \qquad (3)$$

number attached in the standard compound and h' is an empirically determined constant. If the Baker–Nathan effect is something peculiar to hydrogen atoms, h will be, in fact, reasonably constant. If not, then h' will be more nearly constant than h. Table 1 compares h and h' for acid-catalyzed hydrolysis of acetals and ketals, while Table 2 does the same for heats of hydrogenation of monosubstituted and *trans*-disubstituted olefins.

Tables 1 and 2 clearly show that for these reactions at least h is a more nearly constant quantity than h'. Although data from other reaction series are less conclusive,

[1] M. M. Kreevoy and R. W. Taft, Jr., *J. Amer. Chem. Soc.* **77**, 5590 (1955).
[2] R. W. Taft, Jr. and M. M. Kreevoy, *J. Amer. Chem. Soc.* **79**, 4011 (1957).
[3] M. M. Kreevoy and R. W. Taft, Jr., *J. Amer. Chem. Soc.* **79**, 4016 (1957).
[4] R. W. Taft, Jr., *Steric Effects in Organic Chemistry* (Ed. M. S. Newman) p. 556. Wiley, New York (1956).
[5] C. A. Coulson, *Valence* p. 238. Clarendon Press, Oxford (1953).
[6] J. W. Baker and W. S. Nathan, *J. Chem. Soc.* 1844 (1935).
[7] M. M. Kreevoy and H. Eyring, *J. Amer. Chem. Soc.* **79** 5121 (1957).

TABLE 1. COMPARISON OF h AND h' FOR HYDROLYSIS OF ACETALS AND KETALS $R_1R_2C(OC_2H_5)_2$*

R_1	R_2	$\log(k/k_0) + 3{\cdot}60\Sigma\sigma^*$	h	h'
CH_3	H	−1·72	0·57	1·7
iso-C_3H_7	H	−2·62	0·52	2·6
tert.-C_4H_9	H	−2·99	0·50	3·0
$(C_2H_5)_2CH$	H	−2·43	0·49	2·4
H	H	−3·73	0·62	1·9
XCH_2†	H	—	0·57	2·3
XCH_2‡	CH_3	—	0·3 ± ·2	−0·3/0

* Data taken from ref. 1. The standard compound, for which $k = k_0$, $\Sigma\sigma^* = 0$, $n = n_0 = 6$ and $n' = n_0' = 2$, is acetonal.
† Average of seven monosubstituted acetals in which $n = 2$ and $n' = 1$.
‡ Average of seven monosubstituted ketals in which $n = 5$ and $n' = 2$.

TABLE 2. COMPARISON OF h AND h' FOR HEATS OF HYDROGENATION OF OLEFINS $R_1CH = CHR_2$*

R_1	R_2	$\Delta H - \Delta H + 2{\cdot}41\Sigma\sigma^*$	h	h'
H	H	−2·8	0·47	1·4
CH_3	H	−1·3	0·43	1·3
iso-C_3H_7	H	−2·0	0·40	2·0
sec.-C_4H_9	H	−2·1	0·42	2·1
tert.-C_4H_9	H	−2·2	0·37	2·2
XCH_2†	H	—	0·39	1·6
iso-C_3H_7	CH_3	−0·5	0·25	−·5/0
C_2H_5	C_2H_5	−0·5	0·25	−·5/0
tert.-C_4H_9	CH_3	−1·2‡	0·40	−1·2/0
tert.-C_4H_9	tC_4H_9	−2·3‡	0·39	−2·3/0
XCH_2§	CH_3	—	0·27	−·27/0

* These data were taken from ref. 2 except as otherwise noted. The standard compound is *trans*-2-butene, for which $\Delta H = \Delta H_0$, $\Sigma\sigma^* = 0$, $n = n_0 = 6$ and $n' = n_0' = 2$.
† Average of ten monosubstituted compounds in which $n = 2$ and $n' = 1$.
‡ Taken from the data of R. B. Turner, D. E. Nettleton and M. Perelman, *J. Amer. Chem. Soc.* **80**, 1430 (1958); corrected from solution in acetic acid at 25° to the gas phase at 82°.
§ Average of three monosubstituted compounds in which $n = 5$ and $n' = 2$.

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it seems quite likely that we are dealing with a phenomenon in which hydrogen plays a special role, quantitatively, if not qualitatively. This is in accord with the original ideas of Baker and Nathan,[6, 8] based on a qualitative comparison of reactivities.

Table 3 compares h, ρ^* and the average value of ΔH_ψ or ΔF_ψ to which a single $\alpha\beta$-unsaturated substituent gives rise. These values were empirically determined from equations (1) and (2).[3, 9] It seems quite plain that ρ^* is not related in any simple way to h or ΔF_ψ or ΔH_ψ. If the Baker–Nathan effect is closely related to the resonance effects arising from conjugation and if the α-hydrogen bonding model is used, simple theory[7, 9] predicts that h should equal 0·07 times the resonance effect of a single $\alpha\beta$-unsaturated substituent for the first three reactions in Table 3, but should be 0·13 times this resonance effect for the hydrogenation of acetylenes to alkanes. Table 3 bears out this prediction. These facts strongly suggest that the Baker–Nathan effect is related to conjugation, a view which has been widely held since the effect was first recognized.[6, 8, 10]

TABLE 3. INDUCTIVE, CONJUGATION AND BAKER–NATHAN EFFECTS*

Reaction	ρ^*	h	ΔF_ψ or ΔH_ψ†
Acetal hydrolysis	+4·93‡	−0·73‡	7·0
Olefin hydrogenation	−2·41	+0·44	5·5
Carbonyl hydrogenation§	−6·39	+0·54	6·6
Acetylene hydrogenation	−5·06	+0·61	4·7

* Taken from refs. 3 and 9.
† The average value of ΔF_ψ or ΔH_ψ to which a single $\alpha\beta$-unsaturated substituent gives rise.
‡ These values have been multiplied by $-2{\cdot}3\ RT$ to make them comparable with others in this Table.
§ ΔF for the reaction $R_1R_2CH{=}O + H_2 \longrightarrow R_1R_2CHOH$ at 60° in toluene solution, obtained as described in Ref. 2.

Table 4 shows that ΔF_ψ for hydrogenation of carbonyl compounds and ΔH_ψ for hydrogenation of olefins and acetylenes are closely approximated by the change in resonance energy, ΔE_ψ, calculated for the reaction by the LCAO–MO method.[3, 5] Table 5 shows that these calculations are much less satisfactory for estimating the effect of conjugation on the acid-catalyzed hydrolysis rates of acetals and ketals. In these calculations the carbon–carbon π-bond resonance integral (β) was given the value 13·5 kcal/mole and it was assumed that the resonance integral for the carbon–oxygen bond was equal to that for the carbon–carbon π bond.[3] The Coulomb integral for oxygen was given a value larger by 0·5β than that for carbon, but the results are not too sensitive to the values of the Coulomb integrals.

In calculating the resonance energies of the acetal and ketal hydrolysis transition states the transition state was assumed to resemble the product of the rate-determining step, $(R_1R_2COC_2H_5)^{\oplus}$.

[8] J. W. Baker, *Hyperconjugation*. Oxford University Press (1952).
[9] M. M. Kreevoy, unpublished work.
[10] R. S. Mulliken, C. A. Rieke, D. Orloff and H. Orloff, *J. Chem. Phys.* **17**, 1248 (1949).

TABLE 4. RESONANCE ENERGIES OF OLEFINS AND CARBONYL COMPOUNDS[a]

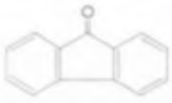
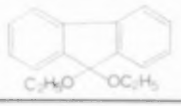
Compound	ΔH_ϕ or ΔF_ϕ (kcal/mole)	ΔE_ϕ (kcal/mole)
Olefins:		
$-CH=CH-CO-$ †	6·2 ± 0·6	6·6
$-CH=CHCH=CH-$ ‡	5·3 ± 0·2	6·3
$C_6H_5CH=CH_2$	4·3	5·8
$C_6H_5CH=CHCO_2CH_3$	11·8	12·8
$C_6H_5CH=CHC_6H_5$	12·5	12·6
$C_2H_5O_2CCH=CHCO_2C_2H_5$	10·1	13·4
$C_6H_5CH=CHCH=CHC_6H_5$	19·1	19·4
Acetylenes:		
$C_6H_5C\equiv CH$	4	5·8
$n\text{-}C_4H_9C\equiv C-C\equiv CnC_4H_9$	10	12·6
$C_6H_5C\equiv C-C_6H_5$	11	12·6
$HOOCC\equiv CCOOH$	12	13·4
$C_6H_5C\equiv C-C\equiv CC_6H_5$	19	19·9
Carbonyl compounds:		
$CH_2CH-CHCHO$	5·1	6·6
$C_6H_5CH=CHCHO$	5·8	7·0
C_6H_5CO- §	6·3 ± 0·6	5·9
$C_6H_5COC_6H_5$	11·0	11·2
	11·2	12·6
	11·5	11·1
$C_6H_5COCO_2\text{-}iso\text{-}C_3H_7$	12·8	11·2

TABLE 5. ACETAL AND KETAL HYDROLYSIS TRANSITION STATE RESONANCE ENERGIES*

Acetal or ketal	ΔF_ψ† (kcal/mole)	ΔE_ψ‡ (kcal/mole)
$CH_3CH{=}CHCH(OC_2H_5)_2$	7·3	11
$C_6H_5CH{=}CH(OC_2H_5)_2$	7·1	12
	7·3	15

* Data taken from ref. 3.
† Empirical value.
‡ Calculated resonance energy of the appropriate carbonium ion with $\beta = 13{\cdot}5$ kcal/mole.

This will be a satisfactory approximation only as long as the product ion is much less stable than the protonated substrate, which is the starting point of the rate determining step.[11] The low empirical values of ΔF_ψ for the acetals and ketals leading to

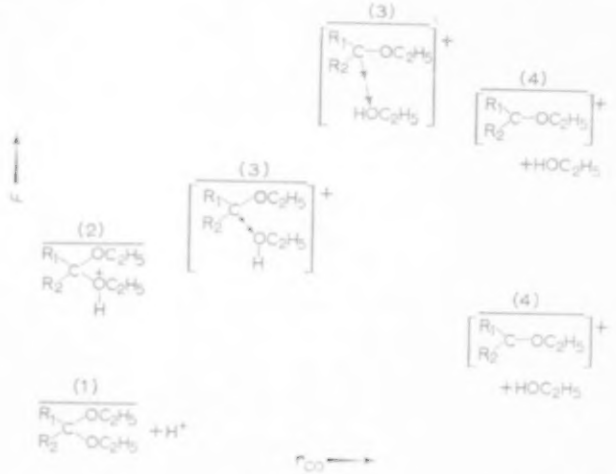


FIG. 1. The energy levels and structure of acetal and ketal hydrolysis transition states and intermediates. State (1) is the starting state. State (2) is the protonated starting state. State (3) is the transition state for a non-conjugated acetal or ketal. State (4) is the carbonium ion intermediate for a non-conjugated acetal or ketal and is the product of the rate-determining step. State (4′) corresponds to state (4) except that it is highly stabilized by resonance. State (3′) is the transition state leading to (4′). The ordinate is free energy per mole and the abscissa is the length of the carbon–oxygen bond which is breaking.

[11] G. S. Hammond, *J. Amer. Chem. Soc.* 77, 334 (1955).

* Data taken from refs. 3 and 9.
† Average of three compounds of the structure shown and all having $\Delta E_\psi = 6{\cdot}6$ kcal/mole.
‡ Average of two compounds of the structure shown and all having $\Delta E_\psi = 6{\cdot}3$ kcal/mole.
§ Average of thirteen compounds of the structure shown and all having $\Delta E_\psi = 5{\cdot}9$ kcal/mole.

more highly stabilized carbonium ions indicates that the transition state for the hydrolysis of these compounds in a resonance hybrid to which the protonated substrate is an important contributor. Conversely the moderately good fit for benzacetal suggests that the ion $(R_1R_2COC_2H_5)^{\oplus}$ is a fair model for the acid-catalyzed hydrolysis of non-conjugated acetals and ketals.[1, 3] The situation is illustrated in Fig. 1.

The good agreement of the empirical and calculated resonance energies of such compounds as diethyl fumarate and acetylenedicarboxylic acid lends strong support to the ρ^*'s calculated from unconjugated compounds. The carbethoxy group σ^* is 2·0 and that for COOH is 2·9 (the groups are strongly electron-withdrawing by an inductive mechanism) so that any serious error in ρ^* would lead to a grossly incorrect value of ΔH_ϕ. For example, Wheland[12] obtained a *negative* resonance energy for diethyl fumarate essentially by setting $\rho^* = 0{\cdot}0$ for the hydrogenation of olefins.

These two examples demonstrate the usefulness of reliable estimates of ΔE_ϕ. Comparison of calculated and observed values of h could be just as useful if reliable calculations can be made.

In the naive LCAO–MO method of calculating resonance energies[5] the π energy levels, E, of a hypothetical non-resonating allyl cation, $C_1 = C_2 - C_3^{\oplus}$, can be calculated from equation (4). The interactions which give rise to the π bond are represented by the non-zero 1,2-resonance integral, β. If interactions between the empty π orbital

$$\begin{vmatrix} -E & \beta & 0 \\ \beta & -E & 0 \\ 0 & 0 & -E \end{vmatrix} = 0 \qquad (4)$$

on C_3 and the π orbital on C_2 are recognized, the 2,3-resonance integral also becomes β, since the ion is symmetrical. Equation (4) then becomes equation (5). The roots of equation (4) are $E = 0 \pm \beta$. Since β is a negative quantity, the total π-electron

$$\begin{vmatrix} -E & \beta & 0 \\ \beta & -E & \beta \\ 0 & \beta & -E \end{vmatrix} = 0 \qquad (5)$$

delocalization energy of the non-resonating allyl cation is 2β. (Putting the two electrons into the lowest possible energy level.) The roots of equation 5 are $E = 0 \pm 1{\cdot}41\beta$ and the calculated total delocalization energy of the resonating allyl cation is $2{\cdot}82\beta$. Subtracting $2{\cdot}00\beta$ from $2{\cdot}82\beta$, the resonance energy of the allyl cation is $0{\cdot}82\beta$.

The facts cited above strongly suggest that a carbon–hydrogen bond adjacent to a π orbital should also be linked to that orbital through a non-zero resonance integral. Since this system is not symmetrical, the resonance integral binding the π orbital to the carbon–hydrogen bond will not be the same as that binding carbon to hydrogen. If H_{12} represents the resonance integral for the carbon–hydrogen bond and H_{23} represents the resonance integral binding the π orbital to the carbon–hydrogen bond, the energy levels of a carbonium ion H_1–C_2–C_3 + will be given by equation (6a) in which:

$$\begin{vmatrix} -E & H_{12} & 0 \\ H_{12} & -E & H_{23} \\ 0 & H_{23} & -E \end{vmatrix} = 0 \qquad (6a)$$

[12] G. W. Wheland, *Resonance in Organic Chemistry* pp. 80 and 85. Wiley, New York (1955).

differences in Coulomb integrals have been neglected. The resonance energy given by equation (6a) is $[(H_{23}^2 + H_{12}^2)^{\frac{1}{2}} - H_{12}]$ and represents the stabilizing influence of a single carbon–hydrogen bond on an adjacent cation. The secular determination shown in equation (6a) can be enlarged in a straight forward manner to give the energy levels and resonance energy if more than one carbon–hydrogen bond is involved. Compounds other than carbonium ions can be dealt with similarly. The resonance energy to which α-carbon–hydrogen bonds give rise is thought to be the cause of the Baker–Nathan effect.

Equation (6) assumes that there is a non-zero resonance integral for the π orbital on C_2 with the sp^3 orbital on C_3 which is holding the hydrogen atom. A particular formulation of this assumption has been called "hyperconjugation" and its consequences extensively explored.[13] Another alternative is to consider a non-zero resonance integral for the π orbital on C_2 with the hydrogen 1*s* orbital. This has been called "α-hydrogen bonding" and produces a secular determinant which is formally equivalent to that in equation (6a).[7]

Hyperconjugation explains most of the features of the Baker–Nathan effect. It has the advantage that, when estimated by equation (7), the resonance integral for the carbon sp^3 orbital with a π orbital on an adjacent carbon atom is substantially larger than that for the π orbital with the hydrogen 1*s* orbital.

$$H_{ab} = \beta \frac{A_{ab} I_{ab} S_{ab}/(1 + S_{ab})}{AIS/(1 + S)} \tag{7}$$

Equation (7) is based on the assumption that the exchange integral is a nearly constant fraction of the bond energy.[14] The parameters A are those of Mulliken.[14] Parameters I are the mean of the ionization potentials of the orbitals making up a bond. The overlap integrals, S, used in this paper are for Slater atomic orbitals and are taken from the tables of Mulliken *et al.*[10] Quantities marked with the subscript *ab* pertain to the bond in question. Others pertain to the aromatic π bond.

Hyperconjugation, however, has the disadvantage that one is hard pressed to explain the particular effectiveness of *hydrogen* atoms, which is clearly shown in Tables 1 and 2.

As an alternative to hyperconjugation we may consider α-hydrogen bonding. α-Hydrogen bonding leads to equation (6b), which differs from equation (6a) only in that the numerical value of H_{13} is not necessarily the same as that of H_{23}.

$$\begin{vmatrix} -E & H_{12} & H_{13} \\ H_{12} & -E & 0 \\ H_{13} & 0 & -E \end{vmatrix} = 0 \tag{6b}$$

α-Hydrogen bonding would represent the Baker–Nathan effect as a sort of minor neighboring group participation,[15, 16] not important enough to lead to major alterations of molecular geometry. It would explain the unique effectiveness of hydrogen,

[13] O. Lofthus, *J. Amer. Chem. Soc.* **79**, 24 (1957). Reference to voluminous work by Mulliken and his co-workers can be found in this paper.
[14] R. S. Mulliken, *J. Phys. Chem.* **56**, 295 (1952).
[15] M. Simonetta and S. Winstein, *J. Amer. Chem. Soc.* **76**, 18 (1954).
[16] S. Winstein and E. Grunwald, *J. Amer. Chem. Soc.* **70**, 828 (1948).

since both theory[7] and experiment[17] indicate that a hydrogen atom interacts more effectively than a saturated carbon atom with a π orbital on a neighboring carbon atom.

Equation (7) gives $H_{13} = 0{\cdot}3\beta$, where β is the aromatic carbon–carbon bond, if the 2,3-interactions are assumed to be those of the π orbital with the hydrogen 1*s* orbital. The Morse function and the spectroscopic properties of C–H indicate that this molecule would retain about 1/4 of its bond energy if stretched to the distance separating C_2 from H_1. It seems plausible, at least, to set $H_{23} = 1/4\beta$ in calculations of α-hydrogen bonding.[7]

The empirical data suggest that the Baker–Nathan effect should be a fairly linear function of the number of carbon–hydrogen bonds adjacent to the π orbital. The calculated resonance stabilization provided by α-hydrogen bonding will be such a function provided that two conditions are satisfied: (1) that H_{23} is small by comparison with H_{12}, and (2) that H_{23} is the same for all of the carbon–hydrogen bonds. For example, if $H_{23} = 1/4H_{12}$, the resonance stabilization of a carbonium ion by a single α-carbon–hydrogen bond is 0·062 H_{23}. With the same assignment of integrals the stabilization of a carbonium ion by six adjacent carbon–hydrogen bonds is $6 \times 0{\cdot}055\ H_{23}$.

The Baker–Nathan effect can be calculated from equations like (6) by calculating the resonance energy of the general starting material (I), the general product (II), the standard starting material (III) and the standard product (IV).

$$\left.\begin{aligned} B &= (\text{II}) - (\text{I}) - (\text{IV}) + (\text{III}) \\ h &= \frac{(\text{II}) - (\text{I}) - (\text{IV}) + (\text{III})}{n - n_0} \end{aligned}\right\} \tag{8}$$

Using $H_{12} = \beta = 14$ kcal/mole and $H_{23} = 1/4\ H_{12}$, a number of average h values have been computed from equation (8) by varying n from 0 to n_0.[7] Those for the reactions

$$R_1R_2C{=}O + H_2 \longrightarrow R_1R_2CHOH \tag{9}$$

$$R_1CH{=}CHR_2 + H_2 \longrightarrow R_1CH_2CH_2R_2 \tag{10}$$

$$R_1C{\equiv}CR_2 + 2H_2 \longrightarrow R_1CH_2CH_2R_2 \tag{11}$$

are compared with empirical values in Table 6.

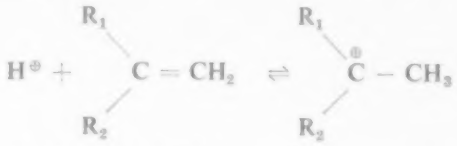
TABLE 6. CALCULATED AND EMPIRICAL VALUES OF h

Reaction	Calcd.	Empirical
9	0·43	0·56 ± 0·06
10	0·43	0·44 ± 0·05
11	0·85	0·61 ± 0·05

[17] G. W. Wheland, *Advanced Organic Chemistry* p. 513. Wiley, New York (1949). The experimental evidence referred to is the high "migratory aptitude" of a hydrogen atom on a carbon atom adjacent to a carbonium ion.

[18] E. Berliner and F. Berliner, *J. Amer. Chem. Soc.* **71**, 1195 (1949); *Ibid.* **72**, 222 (1950).

The calculated h for the formation of a carbonium ion from a saturated compound is −0·80 kcal/mole. The empirical h for acid catalyzed hydrolysis of acetals and ketals is −0·73 kcal/mole. The agreement supports the conclusion, previously suggested on other grounds, that for most acetals and ketals the hydrolysis transition state closely resembles the carbonium ion. On the other hand, the empirical h for solvolysis of *tert.*-carbinyl chlorides in aqueous ethanol at 25° is only −0·34 kcal/mole, which suggests that the solvolysis transition state has substantial resonance contributions involving a covalent bond from a solvent oxygen to the central carbon atom. The calculated h for reaction (12):



(12)

is −(0·80 − 0·43) = −0·37 kcal/mole. It has recently been shown that this is approximately the value of h for the hydration of monosubstituted *iso*butylenes,* $XCH_2C(CH_3) = CH_2$, supporting the conclusion that the transition state for this reaction in some ways resembles the carbonium ion. These examples illustrate the usefulness of equation (6) and the integrals given for the estimation of h.

It is recognized that H_{23} is actually not independent of n. The first α-carbon–hydrogen bond can exert the greatest stabilizing influence because it can assume the ideal position in space, as nearly as possible parallel to the π orbital. A carbon–hydrogen bond lying in the nodal plane of the π orbital will exert no stabilizing influence at all. These effects, however, are probably considerably leveled by rotation about the C_2–C_3 σ bond, so that something of an average effect is actually observed. Much the same thing is true of open-chain conjugated systems. It is thought to be responsible for the lowering of the resonance integral from 18–20 kcal/mole in systems having fixed, ideal, geometry, to 13–14 kcal/mole in open-chain conjugated systems. The use of the latter value for β undoubtedly results in a partial compensation for the non-ideal geometry in α-hydrogen bonding.

A "Baker–Nathan order" has been observed for rates of bromination of compounds

in which R was varied from methyl to *tert.*-butyl. This might very well be due to "β-hydrogen bonding",[7] in which the overlap integral for a π orbital with a β-hydrogen atom is considered to be non-zero.

The most realistic approach to the problem of resonance stabilization due to a carbon–hydrogen bond α to a π orbital is to assume that *both* the resonance integrals mentioned above are non-zero. Such an assumption leads to equation (12)

$$\begin{vmatrix} -E & H_{12} & H_{13} \\ H_{12} & -E & H_{23} \\ H_{13} & H_{23} & -E \end{vmatrix} = 0 \qquad (12)$$

from the ion H_1–C_2–$C_3^{\oplus}$. Since none of the resonance integrals, H_{ab}, in equation (12)

* Unpublished results kindly communicated by Professor R. W. Taft, Jr.

can be reliably evaluated, it is plain that this model can accommodate a wide variety of Baker–Nathan effects for any particular reaction series, so that no single value can be used to test it. If H_{13} is of about the same order of magnitude as H_{23}, this model does make the unique prediction that the Baker–Nathan effect will be far larger for carbonium ion reactions than for carbanion reactions. This prediction can be seen in Table 8, which compares the calculated resonance energies of H_1–C_2–$C_3^{\oplus}$, H_1–C_2–$C_3^{\ominus}$ and H_1–C_2–C_3=C_4. In these calculations it was assumed that $H_{12} = \beta$ and, where needed, $H_{34} = \beta$. All differences in Coulomb integrals were neglected.

TABLE 8. CALCULATED RESONANCE ENERGIES FOR A VARIETY OF H_{13} AND H_{23}

H_{13}	H_{23}	Resonance energy		
		$H_1C_2C_3^{\oplus}$	$H_1C_2C_3^{\ominus}$	$H_1C_2C_3=C_4$
0	0	0·000	0·000	0·000
$1/4\beta$	0	$0·062\beta$	$0·062\beta$	$0·031\beta$
$1/8\beta$	0	$0·016\beta$	$0·016\beta$	$0·008\beta$
$1/4\beta$	$1/4\beta$	$0·225\beta$	0·000	$0·062\beta$
$1/8\beta$	$1/8\beta$	$0·060\beta$	0·000	$0·016\beta$
$1/4\beta$	$1/8\beta$	$0·132\beta$	$0·016\beta$	$0·040\beta$

It can be seen from Table 8 that the predicted resonance energies of carbanions are identical with those of carbonium ions as long as either H_{13} or H_{23} is zero. If the smaller of these is even half of the larger, however, the resonance energy of the carbanion is only a little more than 1/10 of the resonance energy of the carbonium ion. As the difference between the two becomes less, the resonance energy of the carbanion becomes smaller still, while that of the carbonium ion becomes larger. These general conclusions are *independent* of the absolute values of any of the resonance integrals, and also independent of which resonance integral is the larger.

If the magnitude of the Baker–Nathan effect on some carbanion or carbanion-like reactions could be compared with some carbonium ion reactions, an estimate of H_{13}/H_{23} (or H_{23}/H_{13}) could be made. Unfortunately (or fortunately, depending on one's point of view) the required data do not seem to be available for carbanion-type reactions.

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DEUTERIUM ISOTOPE EFFECTS AND HYPERCONJUGATION

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Abstract—There now exists ample published evidence which indicates that reactions with rate-determining steps which involve carbonium ion or partial carbonium ion formation are slowed by the substitution of a deuterium atom for a hydrogen atom in a hyperconjugating position. In each of the several cases where data are available it seems that the isotope *rate* effect is paralleled by an isotope *activation energy* effect although entropy factors also contribute. It seems fairly clear from theory that the isotope activation energy effects can only arise from (a) changes in vibration frequency of the hydrogen and deuterium atoms on activation, (b) tunnelling of the hydrogen atom or (c) anharmonicity effects. The second effect must be unimportant in these reactions although it might be a major factor in reactions where hydrogen bonds are directly broken. Several lines of evidence indicate that anharmonicity effects although small are present and may confuse the quantitative interpretation of the isotope rate effects. Thus the interpretation of secondary isotope rate effects is complicated but the application of the time-honored classical organic chemical method of comparing the effects in a large number of different compounds indicates that hyperconjugation is the predominant cause of these secondary isotope rate effects. If we further assume that the variations in these effects in closely related compounds are due to variations in hyperconjugation, the following conclusions are tentatively indicated: (1) There are steric effects on hyperconjugation. (2) There are substituent effects on hyperconjugation; conjugating and hyperconjugating substituents increase the extent of hyperconjugation of a single C–H bond. (3) There are solvent effects on hyperconjugation.

IT has been known for several years that the replacement of hydrogen in a hyperconjugating position by a deuterium atom generally leads to a diminution in the rate of carbonium ion-type reactions. The author's studies of these phenomena have been concerned with the solvolysis rates of β-deutero-*tert.*-alkyl chlorides,[1, 2, 3] *p*-(α-deuteroalkyl)diphenylmethyl chlorides[4] and α-deuteroketals.[5]

Similar systems which have been studied by other workers include the solvolysis of (1) β-deutero-2-pentyl chlorosulfite, tosylate and bromide,[6] (2) *cis*- and *trans*-β-deutero*cyclo*pentyl tosylates,[7] (3) β-deutero-β-phenethyl tosylate,[8] (4) 1-chloro-1-(*p*-methylphenyl)ethane-2,2,2-d_3 (methyl-*p*-tolycarbinyl chloride) and its *p*-methyl-d_3 analog.[9]

The present paper will briefly review with deductions from the absolute rate theory the possible origins of these isotope effects; critically examine the rather extensive experimental data now available in order to empirically assess in a qualitative fashion

[1] V. J. Shiner, Jr., *J. Amer. Chem. Soc.* **75**, 2925 (1953).
[2] V. J. Shiner, Jr., *J. Amer. Chem. Soc.* **78**, 2653 (1956).
[3] V. J. Shiner, Jr., *J. Amer. Chem. Soc.* **76**, 1603 (1954).
[4] V. J. Shiner, Jr. and C. J. Verbanic, *J. Amer. Chem. Soc.* **79**, 373 (1957).
[5] V. J. Shiner, Jr. and Sally Cross, *J. Amer. Chem. Soc.* **79**, 3599 (1957).
[6] E. S. Lewis and C. E. Boozer, *J. Amer. Chem. Soc.* **74**, 6306 (1952); *Ibid.* **76**, 795 (1954).
[7] A. Streitwieser, Jr., R. H. Jagow, R. C. Fahey and S. Suzuki, *J. Amer. Chem. Soc.* **80**, 2326 (1958).
[8] W. H. Saunders, Jr., S. Asperger and D. H. Edison, *Chem. & Ind.* 1417 (1957).
[9] E. S. Lewis and G. M. Coppinger, *J. Amer. Chem. Soc.* **76**, 4495 (1954).

the relative importance of the several theoretically possible origins and interpret the meaning of these data with respect to some of the problems of hyperconjugation.

Although several others considered the problem earlier, the most extensive theoretical treatments of the effects of isotopic substitution on reaction rate have been made by Bigeleisen[10] and Melander.[11] Each of these authors examined the effects of changing nuclear mass on the parameters in the equation derived from the "theory of absolute rates" and, although the two treatments differ in some details, the results are equivalent. The equation derived by Bigeleisen for the isotope effect may be expressed as follows, neglecting tunnelling:

$$k_H/k_D = K_H/K_D\left(\frac{m_D^*}{m_H^*}\right)^{\frac{1}{2}} \cdot \frac{s_H/s_D}{s_H^\ddagger/s_D^\ddagger} \cdot \prod_i \frac{u_i^\ddagger{}_H/u_i^\ddagger{}_D}{u_{iH}/u_{iD}}$$

$$\prod_i \frac{e^{(u_{iH}-u_{iD})/2}}{e^{(u_i^\ddagger{}_H-u_{iD}^\ddagger)/2}} \cdot \prod_i \frac{(1-e^{-u_{iH}})(1-e^{-u_{iD}})^{-1}}{(1-e^{-u_{iH}^\ddagger})(1-e^{-u_{iD}^\ddagger})^{-1}}$$

where K represents the transmission coefficient, m^* the effective mass of the molecule along the reaction co-ordinate and s the symmetry numbers. Subscripts H and D refer to values for the hydrogen and deuterium compounds, respectively, and the superscript ‡ refers to values for the transition state; values with no superscript refer to the initial state. u_i is defined as $h\nu_i/kT$, where h and k are Planck's and Boltzmann's constants, and ν_i is a molecular vibration frequency. The transmission coefficient ratio may be taken as unity and the symmetry number ratio as unity. Since the reactions under discussion in this paper all involve motions of larger atoms, such as halogen or carbon, the effective reaction mass ratio must be very nearly unity as well. Because the vibrations are assumed to be harmonic and the force constants are equal for both hydrogen and deuterium compounds, $u_{iH}^\ddagger/u_{iD}^\ddagger = u_{iH}/u_{iD}$ and the ratio of these quantities is unity. The isotope effect is then determined essentially exclusively by the last two product factors. The first of these is the zero-point energy term. The second is due to factors coming into play when vibrational levels higher than the zeroth one are occupied and is relatively unimportant at temperatures at or below room temperatures and frequencies of 1000 cm^{-1} or higher where the higher levels are not utilized. Bigeleisen[10] also derived an equation expressing the activation-energy difference between isotopic molecules which may be written, neglecting the temperature coefficient of the transmission coefficient and tunnelling, as:

$$E_H - E_D = \sum_i \left[\frac{e^{u_i}(u_i-1)+1}{(e^{u_i}-1)^2} - \frac{1}{2}\right] h(\nu_{iH} - \nu_{iD})$$

$$- \sum_i \left[\frac{e^{u_i^\ddagger}(u_i^\ddagger-1)+1}{(e^{u_i^\ddagger}-1)^2} - \frac{1}{2}\right] h(\nu_{iH}^\ddagger - \nu_{iD}^\ddagger)$$

at reasonably high values for ν and low values for T:

$$E_H - E_D \approx \sum_i \left[\frac{u_i - 1}{e^{u_i}} - \frac{1}{2}\right] h(\nu_{iH} - \nu_{iD}) - \sum_i \left[\frac{u_i^\ddagger - 1}{e^{u_i^\ddagger}} - \frac{1}{2}\right] h(\nu_{iH}^\ddagger - \nu_{iD}^\ddagger)$$

[10] J. Bigeleisen, *J. Chem. Phys.* **17**, 675 (1949).
[11] L. Melander, *Arkiv Kemi* **2**, 211 (1950).

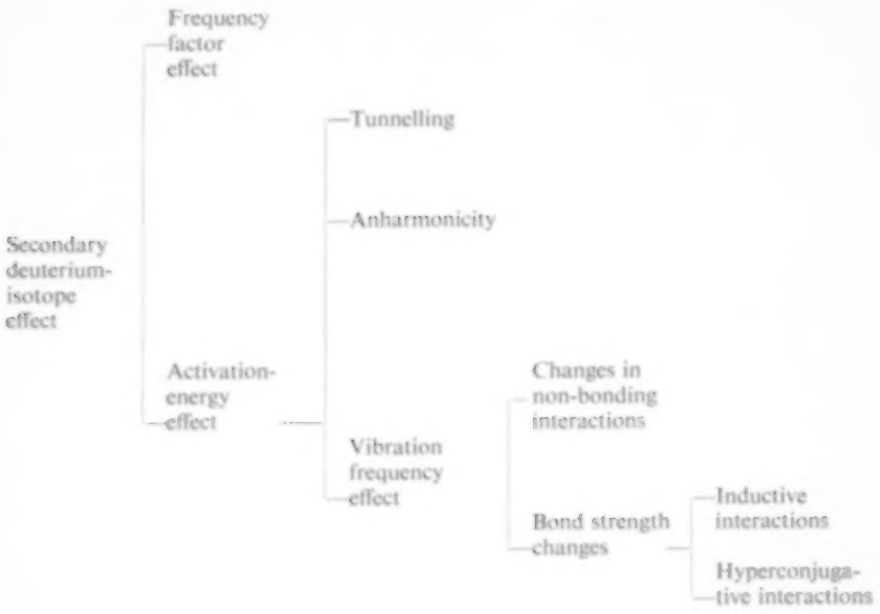
If ν_i is high or T low, the first term in each of the brackets is very nearly zero and the activation-energy difference is due to the difference in the zero-point energy differences in the initial and transition states. If ν_i is low or T high, occupation of the excited vibrational levels becomes significant and the first term in the brackets in each case becomes significant relative to 1/2 and the activation energy is not exactly equal to the difference in the differences in zero-point energies. However, it is important to note that if the frequencies of vibration ν_i do not change on activation ($\nu_i = \nu^{\ddagger}_i$ and $u_i = u^{\ddagger}_i$) then there can be no difference in activation energies between hydrogen and deuterium compounds. Therefore if it is known that deuterium substitution causes a higher activation energy one can be certain that it is due to (1) a lowering of one or more vibration frequencies involving the isotopic atom in the transition state, (2) anharmonicity or tunnelling effects neglected in the above treatment or, much less likely, (3) a temperature coefficient of the transmission coefficient ratio. It also seems impossible that tunnelling effects would be important in those reactions which do not involve C–H bond rupture. Thus an observed isotope activation energy effect means, with the possible exception of anharmonicity effects discussed below, that the vibration frequencies of the isotopic atom change in going to the transition state. This could be due to either bond strength changes or to changes in non-bonding interactions. Bond strength changes may be due either to inductive or hyperconjugative interactions of the isotopic bond with the reaction center. Thus the developing carbonium ion center can withdraw electrons from an adjacent C–H bond, making this bond weaker in the transition state. The bond will therefore have a lower vibration frequency in the transition state and substitution of D for the H will cause the rate to be slower.

Halevi[12] observed that the acid ionization constants of α-dideuterophenylacetic acid and α-dideuterobenzylammonium ion were smaller than those of their protium analogues and suggested that this apparent greater electron release by the C–D bond than the C–H bond is due to anharmonicity and a resulting slight disparity in the mean configurations of the C–H and C–D bonds. These results could be due to the effect suggested or to an inductive effect on the vibration frequencies.[7] More convincing evidence of the role of anharmonicity on the relative ground state electron releasing abilities of C–H and C–D bonds has been given by Tiers,[13] who reports that nuclear magnetic resonance shifts indicate that the fluorine nuclei of the CF_2H group of CF_3–CF_2–CF_2H are less shielded than the corresponding nuclei in CF_3CF_2–CF_2D. Streitwieser[14] has pointed out that the observation of optical activity due solely to differences between D and H, in, for example, CH_3–CH_2–CH_2–CHD–OH,[15] must be due to anharmonicity effects. However, it is difficult to extrapolate from these latter observations and predict what kinetic or equilibrium constant effects should result from such anharmonicity influences. A rather complete theoretical treatment of the isotope effect in the trideuteroacetic acid–trideuteroacetate ion equilibrium, neglecting anharmonicity, should be possible. If this corresponds nearly to the observed values, as Streitwieser[7] suggests is probable, then anharmonicity effects could be judged to be correspondingly small. As Lewis has pointed out in his paper delivered at this Conference, these secondary isotope effects due apparently to inductive interactions are

[12] E. A. Halevi, *Tetrahedron* **1**, 174 (1957).
[13] G. V. D. Tiers, *J. Amer. Chem. Soc.* **79**, 5585 (1957).
[14] A. Streitwieser, Jr., personal communication.
[15] A. Streitwieser, Jr., *J. Amer. Chem. Soc.* **75**, 5014 (1953).

in the direction which make $k_H/k_D < 1$ in the solvolytic reactions and therefore could not alone explain those results.

The origin of the isotope effects as predicted from the theory reviewed in the discussion above are outlined in the following chart:



It can be seen in the above chart that the connection between hyperconjugation and the deuterium-isotope rate effect is a long and complicated one which traces the line along the bottom of the chart from left to right. Isotope activation energy effects due to substitution of deuterium for hydrogen in a hyperconjugating position have been measured for three carbonium ion solvolysis reactions.[3, 4, 9] These values are given in Table 1.

TABLE 1. ISOTOPE ARRHENIUS PARAMETER EFFECTS IN SOLVOLYSIS REACTIONS

Compound	Ea(D)-Ea(H)	log A_D/A_H
$(CH_3)_2CD$-$CCl(CH_3)_2$*	580	0·32
p-CD_3-C_6H_4-$CHCl$-C_6H_5†	100	0·075
p-CD_3-C_6H_4-$CHCl$-CH_3‡	155	0·084

* Ref. 3. † Ref. 4. ‡ Ref. 9.

The results in the first entry in Table 1 are probably more reliable than the other two. Two main conclusions can be reached from the data. First the secondary isotope effects under study are caused in large part by an activation energy effect and secondly

the proportion of the total effect due to the activation energy effect seems to be reasonably constant. Thus the comparison available suggests that in a related series of reactions the isotope rate effects are parallelled by isotope activation energy effects.

Tunnelling effects in these reactions must certainly be small. Similarly changes in non-bonding interactions at the β hydrogens must be small because the only nuclei changing their positions appreciably are at least two atoms removed and the hydrogens on the β positions do not appear from models to be crowded.

Thus the only three remaining effects which might influence the activation energy are anharmonicity, inductive interactions and hyperconjugative interactions. From Halevi's and Lewis's results combined anharmonicity and inductive effects seem to be present, but they are apparently considerably smaller than the total effects observed in the solvolysis reactions and in the opposite direction. Lewis, in his paper delivered at this Conference, has examined extensively by comparing examples of observed secondary isotope effects in a wide range of reactions the connection between hyperconjugation and secondary isotope effects and has concluded that hyperconjugation is one of the important sources of isotope effects. In the remainder of this paper the argument will be pushed a step further and some secondary isotope effect results will be used in a tentative exploratory attempt to study hyperconjugation. The important qualifying assumption that will be used is that the relative magnitudes of the secondary isotope rate effects in the closely related reactions being compared reflect the relative degree of hyperconjugative release of electrons from the isotopically substituted bonds. One important point which needs to be emphasized is that, even if this assumption is true, what is obtained is the relative degree of hyperconjugative electron release from the bonds isotopically substituted and not of the entire group. This limitation takes on added significance now that a number of important papers at this Conference have emphasized that C–C hyperconjugation may and probably does have an importance comparable to C–H hyperconjugation.

TABLE 2. TERTIARY ALKYL CHLORIDE SOLVOLYSES "80%" AQ. ALCOHOL, 25°

	$CH_3-CD_2-\underset{\displaystyle Cl}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-CH_3$	$CH_3-CH_2-\underset{\displaystyle Cl}{\overset{\displaystyle CD_3}{\overset{|}{\underset{|}{C}}}}-CD_3$
k_H/k_D	1·40*	1·77*
	$CH_3-CD_2-\underset{\displaystyle Cl}{\overset{\displaystyle CD_3}{\overset{|}{\underset{|}{C}}}}-CD_3$	$CH_3-\underset{\displaystyle D}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-\underset{\displaystyle Cl}{\overset{\displaystyle CH_3}{\overset{|}{\underset{|}{C}}}}-CH_3$
k_H/k_D	2·35*	1·28†

* Ref. 1. † Ref. 3.

The results summarized in Table 2 show that the β-deuterium rate effect is cumulative as one, two or three of the alkyl groups are deuterated. The results of Streitwieser[7] summarized in Table 3 show in addition that increasing deuteration of a single

TABLE 3. ACETOLYSIS OF *cyclo*PENTYL TOLUENESULFONATES, 50°*

Alkyl toluenesulfonate	k_H/k_D
*trans-cyclo*Pentyl-2-*d*	1·16
*cis-cyclo*Pentyl-2-*d*	1·22
*cyclo*Pentyl-2, 2, 5, 5-d_4	2·06

* Ref. 7.

alkyl group increases the rate effect proportionately. These results are of course consistent with an interpretation based either on inductive or hyperconjugative interactions but more importantly form the basis for dividing the rate effects subsequently quoted into effects per deuterium atom. These are sometimes given as $\Delta\Delta F_a$ per deuterium atom which is $(RT/n)\ln(k_H/k_D)$, where n is the number of deuterium atoms in the deuterated compound or position. By using this method of presentation, the data given in Table 2 can be re-stated as in Table 4 to indicate that methyl substitution on the β carbon carrying a deuterium atom increases the isotope effect.

TABLE 4. TERTIARY ALKYL CHLORIDE SOLVOLYSES "80%" AQ. ALCOHOL, 25°*

Group	$\Delta\Delta F_a$ of deuteration	$\Delta\Delta F_a$ per D
CD_3–	168	56
CH_3–CD_2–	190	95
$(CH_3)_2$–CD–	156	156

* Refs. 1 and 3.

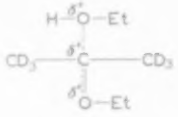
TABLE 5. ACID-CATALYZED HYDROLYSIS OF α-DEUTEROKETALS "90%" AQ. DIOXAN, 25°*

Diethyl ketal of	k_H/k_D	Total obs. $\Delta\Delta F_a$	$\Delta\Delta F^\dagger$ corr.	$\Delta\Delta F_a^\ddagger$	
				per D	in group
Acetone-d_6	1·12	67·2	82·5	14	–CD_3
Methyl ethyl ketone-α-d_5	1·15	83·0	102·6	30	–CD_2–CH_3
Methyl *iso*propyl ketone-α-d_4	1·11	61·9	93·5	51	–$CD(CH_3)_2$
Phenoxyacetone-α-d_3	1·25	132	156·0	57	–CD_2–O–Ø

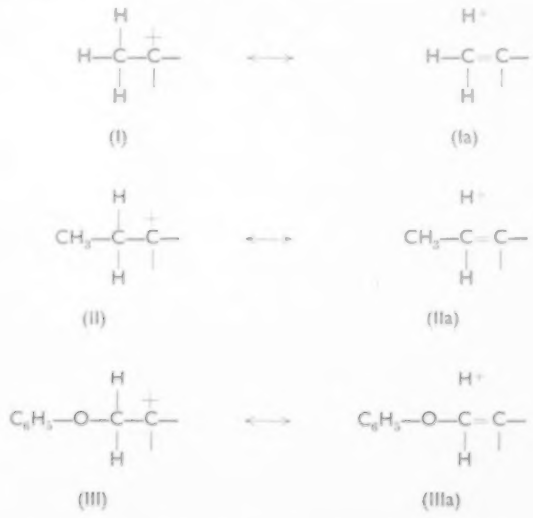
* Ref. 5.
† Corrected to 100% deuteration.
‡ In group other than methyl assuming that the rate effect of deuteration of the methyl group is constant in the series.

Data on the effects of α-deuterium substitution on the rates of hydrolysis of ketals[5] are summarized in Table 5. In the fifth vertical column these data are broken down, assuming that the effect due to deuteration of the methyl group is the same in each compound, into $\Delta\Delta F_a$ values per D atom in each of the different groups.

The first conclusion possible is that the isotope effects in these reactions are less than those observed in the solvolysis of β-deutero-*tert.*-alkyl chlorides. This is presumably due to the smaller degree of vacancy at the carbonium ion center in the transition state which is partially reduced by resonance with the attached oxygen. Thus the transition state approaches a carbonium–oxonium ion hybrid represented by the following structure:



Secondly, we see that the rate effect per D atom varies depending on whether the deuterated group is methyl, ethyl or *iso*propyl in the same general way as was observed in the alkyl chloride solvolyses. In addition the rate effect of deuteration of the phenoxymethyl substituent is large. Therefore β substitution of either methyl or phenoxy groups increases the magnitude of the β-deuterium isotope effect. Since the methyl group is an inductive electron releaser while the phenoxy group is an inductive electron attractor, it would seem that the similar effects of the two groups on the isotope rate effect would be related to their conjugative electron-releasing powers, which operate in the same direction for both but to a greater extent in the phenoxy group. If the isotope rate effects are to be attributed to hyperconjugation, it seems reasonable to attribute the substituent influences on the isotope effects as being due to their stabilizing influences on the hyperconjugating resonance contributing forms:



Thus, owing to the known stabilizing influence of methyl and oxygen substituents on double bonds, (IIIa) should contribute more to the structure of (III) than (IIa) does

to (II), and (IIa) to (II) more than (Ia) does to (I). Therefore the extent of β-C–H hyperconjugation would be (III) > (II) > (I). This is just the order observed in the isotope rate effects.

Further substituent influences on the isotope rate effects have been tabulated in Table 6.[2, 16] Here a single β-alkyl substituent in a tertiary alkyl chloride is varied from methyl to ethyl to *iso*propyl to *tert.*-butyl and the effect of deuteration of both the β-methylene group and a β-methyl group on the solvolysis rate is given.

TABLE 6. TERTIARY ALKYL CHLORIDE SOLVOLYSES "80%" AQ. ALCOHOL, 25°*

R	k_H/k_D for $R-CH_2-\overset{\overset{CH_3}{\vert}}{\underset{\underset{Cl}{\vert}}{C}}-CD_3$	k_H/k_D for $R-CD_2-CCl(CH_3)_2$
Me	1·34	1·40
Et	—	1·37
Pr^i	1·34	1·44
Bu^t	1·40	1·08

* Refs. 3 and 16.

The first column of numbers shows the fairly constant rate effect of methyl deuteration as the halide structure is changed. The difference between 1·34 and 1·40 is just on the borderline of the combined experimental error in these rate measurements and may not be significant. Similarly the vertical column of entries on the right shows the constancy of the effect of methylene deuteration on the rate until the last member where the effect is smaller by a factor of about five. This remarkable absence of an isotope rate effect in the solvolysis of 2-chloro-2,4,4-trimethylpentane-3,3-d_2 has been attributed to the operation of severe crowding in this highly branched structure which prevents the β-C–D or β-C–H bonds of the methylene group from adopting a transition state conformation favorable to their hyperconjugation with the carbonium ion center. It is believed that this steric inhibition of the isotope rate effect provides a striking example of the connection between the isotope rate effects and hyperconjugation and simultaneously important evidence for the concept of steric inhibition of hyperconjugation of a given pair of C–H bonds. It should be noted that, if C–C hyperconjugation is important, the C_3–C_4 bond should be in an optimum configuration for the operation of this effect and the *neo*pentyl group might still show appreciable overall hyperconjugative electron-releasing ability. Saunders has recently observed an interesting confirmation of this effect in the absence of a β-deuterium isotope effect in the solvolysis of β-dideutero-β-phenylethyl tosylate.[8] Here the transition state configuration is apparently fixed by participation of the β-phenyl group. This effect leaves the β-C–H or C–D bonds in a poor conformation for hyperconjugation, as shown in the Newman projection formula on the right:

[16] V. J. Shiner, Jr., unpublished results.

The results of a series of experiments on the isotope effects on solvolysis rates of *p*-deuteroalkylbenzhydryl chlorides[4] are summarized in Table 7. These constants were carefully measured and the rate ratios should be accurate to ± 1 per cent.

TABLE 7. *p*-DEUTEROALKYLBENZHYDRYL CHLORIDES SOLVOLYSES "80%" AQ. ACETONE, 0°*

p-Alkyl group	k_H/k_D
CD_3–	1·06
CH_3–CD_2–	1·025
CH_3–CH(–CH_3)–CD_2–	1·020
$(CH_3)_2CD$–	1·006

* Ref. 4.

The first thing that is noticed is that the isotope effects still operate from a spot which is in a position to hyperconjugate through unsaturated linkages with the reaction center. Thus there must be no changes in non-bonding interactions at this remote site on activation and this factor mentioned above is additionally discounted. Lewis[9] has reported similar effects in *p*-tolylmethylcarbinyl chloride and has in addition observed a very small negative isotope effect ($k_H/k_D < 1$) in *m*-tolylmethylcarbinyl chlorides deuterated in the *meta*-methyl position. Thus the absence of the characteristic isotope effect in the *meta* position and its presence in the *para* position argue strongly that hyperconjugation is a dominant factor in promoting such rate effects. It is to be noted additionally that these *p*-deuteroalkyl effects do not show the same relative orders of magnitude characteristic of the β-deuterium effects. Thus the effect per CD is largest in the methyl, next largest in the ethyl and essentially nil in the *iso*propyl group. These results are suggestive of the operation of some steric hindrance to hyperconjugation in the ethyl, *iso*butyl and *iso*propyl groups. This might be expected to be more important when the alkyl groups are attached to a benzene ring than when they are attached to a carbonium ion because the *ortho*-hydrogens are pointing in a fixed direction out in the plane of the benzene ring. In addition there is less energy gained from hyperconjugation from the remote position and less driving force tending to overcome any steric hindrance to the most favorable conformation. It should be pointed out that the isotope effect would be a measure only of the final situation achieved not mitigated by energy expense necessary to achieve it.

Lastly, several sets of experiments indicate that there are important solvent effects on the β-deuterium and related secondary isotope effects. Some results[4] are shown in Table 8.

Lewis has reported to this Conference some similar observations. Although the electron demand from the reaction center will vary from solvent to solvent and cause

TABLE 8. *p*-METHYL-d_3 BENZHYDRYL CHLORIDE SOLVOLYSES, 0°*

Solvent	k_H/k_D	Relative ρ†	Relative rates
90% aq. alcohol	1·025	0·97	1·0
80% aq. acetone	1·058	0·97	0·14
70% aq. acetone	1·038	0·98	1·0
60% aq. acetone	1·021	1·00	1·9

* Ref. 4.
† The Hammett ρ constant ratio relative to a value of 1·00 for 67% aq. acetone. Determined from the relative rates of benzhydryl chloride and *m*-methylbenzhydryl chloride in the various solvents.

hyperconjugation to vary likewise, this effect must certainly be small in the experiments cited in Table 8. This is indicated by the values of the Hammett ρ constant relative to 67 per cent aq. acetone calculated from the relative rates of benzhydryl and *m*-methylbenzhydryl chlorides in the various solvents. Thus the relative ρ values change insignificantly while the isotope effects change by a factor of almost three. Therefore, solvent interactions at the isotopic site itself seem to be important in influencing these secondary isotope effects. This much is clearly indicated by the data, but not enough evidence is available to allow one to analyze the situation much further and make any conclusive statements about the nature of such solvent influences. The possibility clearly exists that the solvent effects reflect solvent influences on hyperconjugation.

In conclusion I think that the study of secondary deuterium isotope effects has furnished some of the least controvertible evidence for the existence of hyperconjugation influences in transition states. Since there are clearly other sources of secondary deuterium isotope rate effects, the data must be interpreted with extreme care. However, detailed analyses indicate that hyperconjugation influences account for the major part of the observed β-deuterium and related isotope effects on solvolysis reactions. Assuming that the variations in these effects in closely related reactions are due to variations in hyperconjugation, the following conclusions are tentatively indicated:

(1) There are steric effects on hyperconjugation.

(2) There are substituent effects on hyperconjugation; conjugating and hyperconjugating substituents increase the extent of hyperconjugation by a single C–H bond.

(3) There are solvent effects on hyperconjugation.

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CONJUGATION AND HYPERCONJUGATION: A SURVEY WITH EMPHASIS ON ISOVALENT HYPERCONJUGATION

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Abstract—Various aspects and examples of conjugation and hyperconjugation are surveyed, and the desirability of an explicit classification of both conjugation and hyperconjugation into two major types, isovalent and sacrificial (ordinary) is emphasized. The existence of a third type, pluvalent conjugation, is also mentioned. Further, the desirability of a subclassification of isoconjugation and isohyperconjugation each into three sub-types (dative, non-dative, and homodative, in orderof increasing conjugative stabilization) is pointed out, with examples. Sacrificial conjugation and hyperconjugation are usually non-dative, but some examples of dative conjugation and hyperconjugation are cited. The intrinsic jointness of the inductive and mesomeric effects (both of which are forms of resonance) in homodative isoconjugation and isohyperconjugation is emphasized. Homodative alkyl isohyperconjugation in carbonium ions is discussed extensively, with especial reference to McCaulay's Conference paper. Some hitherto incompletely published theoretical evidence, supported by experimental spectroscopic evidence, that the ethylene positive ion is partially twisted in its ground state, is presented; the twist is due to incipient isohyperconjugation.

Definitions of the term hyperconjugation are considered with some care. It is suggested that the Baker–Nathan effect (in so far as it refers to differences between C–H and C–C hyperconjugation) should not itself be described as hyperconjugation, but rather as *differential* hyperconjugation. It is pointed out that there are no obvious theoretical reasons for expecting radical differences in stabilization energy or in magnitude of electron release between C–C and C–H hyperconjugation. Finally, the writer wishes to apologize if he has sometimes gone astray in this paper because of the superficiality of his acquaintance with the vast literature of organic chemistry.

I. INTRODUCTION

(*a*) *General remarks*

MULLER and the writer in a recent paper[1] have shown by modified Hückel-type LCAO–MO (LCAO molecular orbital) calculations how the observed relatively large stabilization energies in alkyl radicals and ions (relative to CH_3 and CH_3^+) can be understood in terms of hyperconjugative π-electron resonance. In seeking to understand the large size of the effects, they found it very illuminating to introduce a classification of hyperconjugative (and of conjugative) effects in terms of types of major VB (valence-bond) resonance structures. Although these structures are in general very familiar,[2] it was felt that a systematic classification and terminology would be of real value.

Although corresponding LCAO and VB structures are only roughly equivalent, the equivalence is probably usually good enough to form the basis for a qualitative classification which should be significant for both. Although the LCAO method is more useful for quantitative calculations, one can much more easily obtain fairly

[1] N. Muller and R. S. Mulliken, *J. Amer. Chem. Soc.* **80**, 3489 (1958).
[2] G. W. Wheland, *Resonance in Organic Chemistry*. Wiley, New York (1955).

reliable qualitative[3] insight into the reasons for the magnitudes of π-electron resonance effects in various kinds of cases by writing corresponding VB resonance structures. (But see Section III(a), Notes added 20 November 1958).

The present paper contains a further development of the classification of conjugated and hyperconjugated molecules in terms of VB resonance structures, with examples. Since this paper was prepared in final form *after the Conference*, advantage has been taken of the opportunity to include in the discussion of examples commentaries[4] on some of the papers presented by others at the Conference.

In view of Dewar's strong advocacy at the Conference of the idea that the effects of π-electron resonance in ordinary conjugation, hence all the more so in ordinary hyperconjugation, are inconsequential, one might be persuaded that any further use of the idea of hyperconjugation has become superfluous. However, as is set forth in a separate complementary paper* the writer is very doubtful that such an extreme viewpoint can be justified. Moreover, a major point in the present paper is that isovalent hyperconjugation should be a much stronger effect than ordinary hyperconjugation, because of resonance akin to that in benzene. On the whole, it seemed best not to consider the impact of Dewar's new ideas in the present paper, except incidentally. Resulting doubts and reasonable modifications of usual ideas will be examined more carefully in the separate paper mentioned.

(b) *Definitions of conjugation and hyperconjugation*

A variety of phenomena in unsaturated and aromatic organic molecules, including those historically referred to as conjugation, have been explained in quantum-mechanical VB theory in terms of π-electron resonance between two or more classical VB structures. The use of the term conjugation has in recent years been increasingly extended to include all molecules believed to be stabilized by π-electron resonance; for example to benzene with its two equivalent Kekulé structures and to aniline with its quinoid in addition to Kekulé structures. In the present paper the word conjugation will be used in this broadened sense. *Conjugation* is then said to exist in a molecule when the principal classical structure or structures contain single bonds each interposed between two multiple bonds or having on one side a multiple bond and on the other a lone π electron, π-electron pair or quartet, or π-electron vacancy. (For conjugation in the cumulenes—see Section III(a)—a slight extension of this definition is needed.)

Hyperconjugated molecules can be defined similarly if we regard a pair or triplet of bonds from an atom e.g. $\left(\begin{matrix}R\\R'\end{matrix}\!\!>\!C \text{ or } \begin{matrix}R\\R'\\R''\end{matrix}\!\!>\!C\right)$ as a quasi-double or quasi-triple bond $\left(\begin{matrix}R'\\R\end{matrix}\!\!>\!C \text{ or } \begin{matrix}R\\R'\\R''\end{matrix}\!\!>\!C\right)$. *First-order hyperconjugation* can be said to exist when the

* R. S. Mulliken, *Tetrahedron* (1959) in press.

[3] However, quantitative factors, which are automatically taken into account in the LCAO-MO method (though not very accurately unless refined forms of the method are used), can sometimes become so important as to seriously modify or even outweigh conclusions based on qualitative insight from VB structures.

[4] Thus the present paper incorporates (a) material prepared before the Conference; (b) responses to ideas and material presented by others at the Conference; (c) some improvements, refinements, and modifications resulting from the stimulus of the Conference papers and discussions. Finally (d) some additional comments believed important were inserted on 20 November 1958.

principal classical structure or structures contain single bonds interposed between one quasi-multiple bond and either an ordinary multiple bond, a lone π electron, π electron pair or quartet, or π-electron vacancy [with a slightly extended definition for cumulenes—see Section III(a)]. *Second-order hyperconjugation* involves single bonds interposed between two quasi-multiple bonds; recent calculations[5] indicate that the effects of second-order hyperconjugation should be quite small.

In the discussion of unsaturated or aromatic molecules with a planar skeleton of the unsaturated and directly attached atoms, the x direction will always be taken in this paper to be perpendicular to the skeletal plane. Then in any quasi-double bond, one is a quasi-σ and one a quasi-π_z or quasi-π_y. Hereafter these will be designated as $[\sigma]$ and $[\pi_z]$ or $[\pi_y]$ bonds.

For a group $H_2=$ or $R_2=$ (as for example in $H_2=CO$ or $R_2=CO$), let the bond orbitals of the two H atoms or of those R atoms which form the quasi-double bond be called a and b. Then the $[\sigma]$ GO (group orbital) has the form $a + b$, the $[\pi_z]$ or $[\pi_y]$ orbital the form $a - b$ (omitting a normalizing factor in each case).

FIG. 1.

For a group $H_3\equiv$ or $R_3\equiv$, letting the three H_3 or R_3 bond orbitals of the quasi-triple bond be called a, b, c, the $[\sigma]$ GO has the form $a + b + c$, while the $[\pi_z]$ and $[\pi_y]$GOs are of the forms $a - b$ and $c - \frac{1}{2}(a + b)$, or *vice versa* (omitting normalization factors and neglecting overlap effects) or suitable orthogonal linear combinations of these, depending on how the triangle abc (see Fig. 1) is oriented with respect to rotation around the $R_3\equiv$ bond. However, the hyperconjugative action is independent of the angle of such rotation. (This is no longer quite true for composite groups $\left.\begin{matrix}R'\\R\end{matrix}\right\} = \text{ or } \left.\begin{matrix}R\\R'\\R''\end{matrix}\right\}\equiv$, insofar as the different R's are unlike in their hyperconjugative effectiveness.)

II. ISOVALENT CONJUGATION AND ISOVALENT HYPERCONJUGATION

(a) *General characteristics; subclasses; interrelations of inductive and mesomeric effects*

In *isovalent conjugation* (or *isoconjugation* if one wants a briefer term) there are two or more classical structures containing equal numbers of π bonds, also of σ and of total bonds. The writer feels that it is worth while, and important,[6] to distinguish

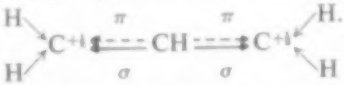
[5] C. A. Coulson and V. Crawford, *J. Chem. Soc.* 2052 (1953); A. Lofthus, *J. Amer. Chem. Soc.* **79**, 24 (1957).

[6] Of course everyone knows these types, and perhaps most chemists will think it silly or presumptuous to give them names, but the writer is convinced that their overt recognition should make it easier to think clearly about them.

three main sub-classes of isovalent conjugation, namely (listing them in order of increasing expected resonance energy), (1), *dative*, (2), *non-dative*, and (3), *homodative*. Typical examples are the following: (1) for the dative subclass, chlorethylene: isovalent dative structure $H_2C^- - CH = Cl^+$ in addition to main structure $H_2C = CHCl$; or chloracetylene; (2), for the non-dative subclass, benzene and the allyl radical: *two equivalent* isovalent structures each; (3), for the homodative subclass, allyl ion or amidinium ion, or their derivatives: two equivalent isovalent structures each, with stabilization not only by resonance per se but also by *necessarily concomitant*[7] partial uniformization of π charge distribution, brought about by the dative action involved in a shift from one of the two isovalent resonance structures to the other (e.g. $H_2C^+ - CH = CH_2$ to $H_2C = CH - C^+H_2$). Two familiar further examples of dative isoconjugation (here *superposed* on benzenoid isoconjugation) are chlorobenzene and aniline, with dative isovalent structures $C_6H_5^- = Cl^+$ and $C_6H_5^- = N^+H_2$ respectively.

Dative isoconjugation involves *exclusively one-way* π dative action, which costs energy in creating an (often long) dipole, so that the dative structure, although isovalent with the main structure, is non-equivalent. On the other hand, homodative isoconjugation releases electrostatic energy by charge redistribution (equalization) as an *intrinsic part* of the total energy release by isovalent π-electron resonance. The resulting bond and charge distribution in the allyl ion may be summarized by $H_2C^{+\frac{1}{2}} = CH = C^{+\frac{1}{2}}H_2$.

But also, in the presence of either dative or homodative isoconjugation, *additional* "inductive" shifts of charge via both σ and π bonds must of course occur. In the dative case, they serve to lower the energy of the dative resonance structure very considerably and thus increase its importance for the molecule; for example in CH_2CHCl, $H_2C^- \xrightarrow[\sigma]{} CH \overset{\pi}{=} Cl^+$ would much better describe the dative structure than $H_2C^- - CH = Cl^+$; then in the actual molecule, when both the isovalent resonance structures have been included, the Cl atom has lost π charge but gained σ charge.

In the homodative case, inductive effects serve to distribute some σ and also some π-electron positive charge to *all* the atoms in the molecule; the resulting distribution might be described by  A major part of the π-electron "inductive" redistribution, as compared with a single VB resonance structure, had, however, already been accomplished by isovalent resonance. Further, it should be especially noted that LCAO-MO π-electron calculations, in contrast to the usual VB formulations, automatically take into account *all* "inductive" as well as mesomeric *π-electron* charge shifts if allowance is made in the calculations for the effect of its charge on the π-electronegativity of each carbon atom.

In isovalent *hyperconjugation* (or isohyperconjugation), as in isoconjugation, there are in VB theory two or more resonance structures containing equal total numbers of bonds, and also containing equal numbers of σ and π bonds if one counts $[\sigma]$ and $[\pi]$ bonds as σ and π bonds. Further, three main sub-classes of isohyperconjugation can usefully be distinguished, namely, (1), dative, (2) non-dative, and (3)

[7] L. Goodman and H. Shull, *J. Chem. Phys.* **23**, 33 (1955). For discussion of the corresponding phenomena in *hyperconjugation*, see references 1 and 11.

homodative; the characteristics of these classes parallel those of the corresponding sub-classes of isoconjugation.

Isohyperconjugation differs from isoconjugation in that there are two (or in general two sets of) isovalent structures which differ (and hence are always non-equivalent) in a certain special way. Namely, the subordinate isovalent structures have *one more ordinary π bond and one less* [π] *bond* than the predominant structures; that it is the former which are subordinate is indicated by experimental evidence and justified by the belief that [π] bonds are very considerably stronger than ordinary π bonds.

(b) *Dative isohyperconjugation* (*and some new notation*)

Let us first consider some examples from the dative sub-class, beginning with CH_3OH. The two isovalent structures are $H_3{\fallingdotseq}C{-}\ddot{O}H$ and $H_3{}^{-}{=}C{\doteq}O^{+}H$ The symbol $\doteq$ represents a π_x bond and the symbol $=$ represents a π_y bond.[1] This or equivalent symbolism is useful in keeping track of π_x and π_y bonds when both types are present, as is very frequently the case when one considers isovalent resonance structures in hyperconjugation.

Even in conjugation, such symbolism is useful for a clear understanding whenever triple bonds, or cumulated bonds, are present: for example $HC{\equiv}C\ddot{\underset{\cdot\cdot}{Cl}}$, with two dative isovalent resonance structures $HC^{-}{=}C{\doteq}\ddot{\underset{\cdot\cdot}{Cl}}^{+}$, $HC{\doteq}C{=}\ddot{Cl}_{+}$ of equal importance, and a third less important one; allene with the single structure $H_2C{\doteq}C{=}CH_2$, or in more detail, $H_2{=}C{\doteq}C{=}C{\doteq}H_2$; phenylacetylene with main structures like $C{\equiv}CH$. This symbolism can of course be omitted whenever it is more trouble than it is worth.

Dative isohyperconjugation should occur in $(CH_3)_2O$ in a way similar to that in CH_3OH: $(H_3{\equiv}C{-})_2\ddot{O}$, $H_3{}^{-}{=}C{=}O^{+}Me$, $MeO^{+}{=}C{=}H_3{}^{-}$. CH_3NH_2, $(CH_3)_2NH$, and $(CH_3)_3N$ insofar as they may be treated as having a nearly planar arrangement of atoms bonded to the nitrogen present again a similar situation. Dative isohyperconjugation is again expected in CH_3Cl, the main structure being $H_3{\equiv}C{-}Cl$, the main subordinate structures $H_3{}^{-}{=}C{\doteq}Cl^{+}$ and $H_3{}^{-}{\doteq}C{=}Cl^{+}$. Dative isohyperconjugation here is closely analogous to dative isoconjugation in chloracetylene. The foregoing examples illustrate how conjugation or hyperconjugation can be either *one-dimensional* (π_x only), or *two-dimensional* (both π_x and π_y). Another interesting example is H_2CO, with isovalent structures $H_2{=}C{\doteq}O$ and $H^{-}{-}C{\equiv}O^{+}$.

In the foregoing examples the effects of isohyperconjugation are doubtless small, first because they are dative (and the effects even of dative *conjugation* are relatively moderate), and second because they are hyperconjugative. The writer sees no sufficient reason, however, to assume that they are entirely negligible.

Another interesting example is that of H_2O_2, where on the basis of spectroscopic evidence[8] the two H–O–O bonds are in planes nearly perpendicular to each other. It is easily shown that a planar structure, either *cis* or *trans*, offers no possibility of isovalent hyperconjugation; only ordinary hyperconjugation is then possible. If steric repulsions between the two H atoms were a determining factor, the planar *trans* form should be preferred. For a 90° twisted form, dative isohyperconjugation can occur to its maximum possible extent. Besides the main structure, , two

[8] E. Hirota, *J. Chem. Phys.* **20**, 136 (1958), and references cited therein.

dative isovalent structures, $O{=}O^{+}\!\!\begin{matrix}H^{-}\\ \diagup\\ \diagdown\\ H\end{matrix}$ and $\begin{matrix}H\\ |\\ O\end{matrix}{}^{+}\!\!\rightleftharpoons OH^{-}$ can be written. If we neglect the fact, whose effect here should be minor, that the HOO angles are somewhat greater than 90°, the left-hand OH bond is formed by a π_z oxygen electron leaving a π_y (and an *s*) lone pair on the atom, while the right-hand OH bond is formed by a π_y oxygen electron leave a π_z lone pair on that atom. By dative action, either a π_z or a π_y O=O double bond can be formed, as indicated in the isovalent structures above. Unfortunately this example cannot be used as a proof of the decisive importance of isovalent hyperconjugation, since π-electron non-bonded repulsions *also* favor the twisted form.[9] Further, the actual twisted form according to Hirota's analysis[8] is only 1·29 kcal more stable than the planar *cis* form (and 0·59 kcal more stable than the planar *trans* form).[8] Another similar example is that of N_2H_4, where again the stable configuration is a twisted one which again is favored both by non-bonded repulsions[9,10] and by isovalent hyperconjugation. In contrast, the planar structure of C_2H_4 is strongly stabilized by π_z-electron bonding although the twisted form would be favored by isovalent hyperconjugation. In $C_2H_4^{+}$, the latter apparently becomes partially dominant, causing twist. (The cases of C_2H_4 and $C_2H_4^{+}$ will be discussed below.)

A final example of dative isovalent hyperconjugation where the effects may be larger is that of boron trimethyl. The main structure is $B(-C{\equiv}H_3)_3$, and there are three isovalent structures of the type $Me_2B{=}C\rightleftharpoons H_3^{+}$. The fact that BMe_3 does not dimerize like BH_3 suggests that it has special stability in itself, due to isovalent hyperconjugation, which is not possible in BH_3. One may of course argue that the CH_3 group cannot replace an H atom in the diborane bridge, but, (a), there is no theoretical reason why it cannot and (b) in Al_2Me_6 with structure analogous to diborane, the methyl group does function as a bridging agent.[10] To be sure, $Me_2BH_2BMe_2$ is known, suggesting that H but not Me can function in a bridge bond; but the dimerization of Me_2BH might also be explained by the lesser amount of hyperconjugation possible here; and/or H may be a *better* bridging agent than Me. Theoretical computations on hyperconjugation in BMe_3, for example by the Hückel method using reasonable empirical parameters, and with due allowance for the presence of strong B^{+}–C^{-} σ bond polarities ("inductive effect"), would be of much interest.

(c) *Non-dative isohyperconjugation*

If its geometry conforms approximately to its conventional formula, as seems probable, the ethyl radical is a typical example of non-dative isohyperconjugation.[1] The main structure is then $H_3{\equiv}C$–$\dot{C}H_2$, with an odd π_z electron on the CH_2 carbon. The hyperisovalent resonance structure is $H_3^{\cdot}\rightleftharpoons C{=}CH_2$, with a quasi-$\pi_z$ odd electron on the H_3. (This is equivalent to $\begin{matrix}H^{\cdot}\\ H{-}C{=}CH_2\\ H\end{matrix}$, as the hyperconjugation resonance structure is often written, provided, of course, suitable resonance among three such forms is understood.) The isopropyl and *t*-butyl radicals furnish similar examples.[1] Another example, ethylene twisted through 90°, will be discussed below. Alkyl-substituted triphenylmethyl radicals, on the other hand, furnish examples where

[9] W. G. Penney and G. B. B. M. Sutherland, *J. Chem. Phys.* **2**, 492 (1934).
[10] R. S. Mulliken, *Chem. Rev.* **41**, 207 (1947).

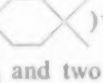
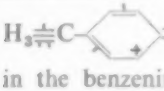
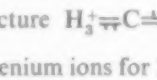
isohyperconjugation, though theoretically expected, is apparently unimportant, but for reasons which appear understandable (see footnote 33).

(d) *Homodative isohyperconjugation*

The alkyl and the aromatic carbonium ions furnish numerous examples of homodative isohyperconjugation. In agreement with experimental evidence, the energy effects of isovalent hyperconjugation should be at a maximum in the homodative subclass. LCAO-MO computations on the alkyl ions (assuming conventional geometry) have been presented by Muller and the writer.[1] Taking the ethyl cation as a typical example, the main structure is $H_3 \overset{+}{\underset{\pi\pi}{\rightleftharpoons}} C \rightarrow C^+ \overset{}{\underset{\pi\pi}{\rightleftharpoons}} H_2$, the hyperisovalent resonance structure is $H_3^+ \overset{}{\underset{\pi\pi}{\rightleftharpoons}} C \overset{+}{=} C = H_2$. Arrowheads have been added to indicate inductive effects; for the π_x electrons, these are automatically included in the LCAO computations (cf. Section II (a) for a fuller discussion in the analogous case of homodative isoconjugation). In our paper, we also included π_y inductive effects because we allowed for π_y as well as π_x hyperconjugation. (Here π_y hyperconjugation is of the ordinary, not isovalent type.)

A related example would be that of the ethyl anion.

The carbonium ions derived from benzene and alkylated benzenes by addition of a proton have been extensively studied by McCaulay and by Kilpatrick, and their collaborators, and those from polycyclic aromatic hydrocarbons by Mackor *et al.*[11] Semi-empirical LCAO computations on the simplest of these, the benzenium ion $C_6H_7^+$, indicate that homodative isohyperconjugation between three ring-positive isovalent structures of the type and two hyperisovalent Kekulé-type structures should strongly stabilize the ion.[12] Let us call this Kekulé hyperconjugation.

In all the methylated (or alkylated) benzene carbonium ions, the same type of isohyperconjugation should occur, *plus* methyl (or alkyl) isohyperconjugation involving homodative transfer of π-electron positive charge to the methyl (or alkyl) groups.[13] The simplest case is that of the toluenium ion. This should exist in six *isomeric forms*[14] depending on which of ring atoms 1 to 6 accepts the proton. Let us consider the 4-toluenium ion  , with its three isovalent ring-positive structures such as  and two isovalent Kekulé-hyperconjugation structures, just as in the benzenium ion, and *in addition* one isovalent methyl-hyperconjugation structure  . Isovalent methyl hyperconjugation is possible in toluenium ions for 2, 4, or 6 addition of the proton; less stable isomers with the added

[11] E. L. Mackor, G. Dallinga, J. H. Kruizinga and A. Hofstra, *Rec. Trav. Chim. Pays-bas* **75**, 836 (1956); E. L. Mackor, A. Hofstra and J. H. van der Waals, *Trans. Faraday Soc.* **54**, 66, 186 (1958); and numerous other papers.

[12] N. Muller, L. W. Pickett and R. S. Mulliken, *J. Amer. Chem. Soc.* **76**, 4770 (1954). Note that all π-electron inductive effects are automatically included (cf. discussion in Section II(b) of the analogous situation in homodative isoconjugation).

[13] D. A. McCaulay and A. P. Lien, *J. Amer. Chem. Soc.* **73**, 2013 (1951); D. A. McCaulay's, *Tetrahedron*. This issue.

[14] The word "isomeric" is not strictly appropriate here, since some of the forms are indistinguishable. But its use, in this section, will be very helpful in making things clear.

proton in the 1, 3, or 5 position should exist but without methyl isohyperconjugation, hence with stability about like the benzenium ion. Attribution of the observed increasing base strengths of increasingly methylated benzenes to methyl hyperconjugation, as proposed by McCaulay,[13] by no means necessarily implies that this is more effective than Kekulé hyperconjugation. The latter (which is equally present[15] in *all* the methylated benzenes, and for *all six* isomers of each) should be present as a more or less constant background factor in all, supplemented by methyl hyperconjugation to an extent which depends on the numbers and positions of the substituted methyl groups. Although the basicity of benzene is very low, it seems entirely likely that the Kekulé hyperconjugation may be of predominant importance in creating a *minimal* basicity in benzene which is then *enhanced* to notable levels of strength by successive increments of methyl hyperconjugation. Theoretical computations by the LCAO-MO method on methylated benzenes would be of great interest in this connection.

As already noted, each carbonium ion derived from benzene or any methylated benzene by protonation can exist in six isomeric forms. For *each* of these isomers, methyl isohyperconjugation with some definite number M of methyl groups, from zero to a maximum of three, can occur, as one can see by drawing VB structures and keeping only those which are isovalent with the ring-positive and Kekulé-hyperconjugated structures.[16] If isohyperconjugative stabilization is the main determining factor, the basicity of any methylated benzene should depend primarily on the *largest M value* possessed by *any of the isomers* of its carbonium ion, and should be greater for larger maximum M; isomers with less than the largest M for that particular molecule should count very little for its basicity, because of their lower stability. On the other hand, the basicity should be greater the greater the *number* N of isomers of *maximum* M.

Table 1 lists the numbers of isomers of each M type for each of the methylated benzenes, and also gives the relative basicity as reported by McCaulay in his Conference paper. It will be seen that the various molecules fall into groups in which the basicity is indeed primarily governed by the maximum M which appears for any of its isomeric forms, and also increases somewhat with the N value for maximum M. The striking increases in basicity from *p*- and *o*-xylene to *m*-xylene and to mesitylene parallel an increasing maximum M.

Inspection of Table 1 shows that an additional factor also somewhat influences basicity. In parentheses following the number N of isomers for any M type for any carbonium ion, in Table 1, is a number (say n) which says how many of these isomers have the added proton attached to the same ring atom as a methyl group. It will be seen that basicity increases somewhat as n/N for the *maximum-M* isomers increases. For example, the mesitylene, isodurene, and pentamethylbenzene carbonium ions all have the same $N(3)$ for the same maximum M (3) but with $n = 0$, 1, and 2 respectively; and the basicity increases with n/N. The hexamethylbenzene carbonium ion has $N = 6$ for its maximum M (again 3) but now $n/N = 1$ since the added proton is necessarily attached to a methyl-bearing ring carbon in *all* isomers. Both effects evidently

[15] Except that proton addition to methylated ring atoms (which should certainly occur) may be somewhat more (or less) effective than to non-methylated ring atoms: half-CC instead of all-CH hyperconjugation.

[16] Additional hyperconjugated structures having one less valence bond (*ordinary* hyperconjugation) although left out of account here, may perhaps also have *some* influence in determining basicity.

TABLE 1. NUMBERS N OF ISOMERS OF METHYLATED-BENZENE CARBONIUM IONS BELONGING TO VARIOUS M TYPES (first four columns of numbers; see text for explanation of M).

Each number N is followed by a second number n in parentheses which tells how many of the N isomers have the proton attached to a methyl-bearing ring carbon. The basicity (last four columns of numbers from McCaulay's Conference paper[13]) is seen to be determined essentially only by those isomers which have maximum M (indicated in the first four columns by bold face type).

					Basicity (McCaulay) and Type			
	$M=0$	$M=1$	$M=2$	$M=3$	$M=0$ (very small)	$M=1$	$M=2$	$M=3$
Benzene	**6(0)**							
Toluene	**3(1)**	**3(0)**				(0·01)		
p-Xylene		**6(2)**				1		
o-Xylene		**6(2)**				2		
m-Xylene	**3(2)**		**3(0)**				20	
Mesitylene	**3(3)**			**3(0)**				2800
Pseudocumene		**3(2)**	**3(1)**				40	
Durene			**6(4)**				120	
Prehnitene			**6(4)**				170	
*iso*Durene		**3(3)**		**3(1)**				5600
Pentamethylbenzene			**3(3)**	**3(2)**				8700
Hexamethylbenzene				**6(6)**				89000

increase the basicity. The enhancement of basicity associated with attachment of a proton to a methyl-bearing ring carbon may reasonably be explained as due to inductive stabilization of isomers of this type, consequent on release of some negative charge by the methyl carbon to the ring carbon to which it is attached.

Further minor factors somewhat influencing the basicity of aromatic carbonium ions perhaps include steric effects, ordinary hyperconjugation,[16] the presence of isomers with less than maximum M values, differences in solvation effects, and perhaps others.

It is of interest that Table 1 indicates that the basicity of toluene, too small to be accurately determined but estimated as 0·01 by McCaulay, should be considerably larger (say about 0·3) to be consistent with the rest of Table 1.

(e) *Isohyperconjugation in* 90°*-twisted ethylene and in* $C_2H_4^+$.

Ethylene with the two CH_2 planes twisted to perpendicularity ("perp. C_2H_4") was perhaps the first recognized example of hyperconjugation, although the name was not then used. Later Roothaan and the writer made a series of LCAO-MO computations on ethylene in its ground state and three excited states, and on $C_2H_4^+$, for angles of twist ϕ ranging from 0° (planar) to 90°.[17] Semiempirical parameter values similar to those used in more recent computations[5] were used, and the effect of π-electron overlap was included. Both π_x and π_y hyperconjugation were taken into account, as becomes obviously necessary as $\phi \to 90°$. Our 1947 paper was intended to be preliminary, and failed to report certain details of our computations. Some of the results on $C_2H_4^+$ which are of particular interest in the present connection will be reported below.

For planar C_2H_4, the VB structure is $H_2C{=}CH_2$, or if one wishes to consider π_y hyperconjugation (which is second-order, and *not* isovalent), $H_2\overline{\overline{\pi}}C{=}C\overline{\overline{\pi}}H_2$. For perp. C_2H_4, the main VB structure $H_2\overline{\overline{\pi}}\dot{C}\text{–}\dot{C}{=}H_2$ is in resonance with the two

[17] R. S. Mulliken and C. J. Roothaan, *Chem. Rev.* **41**, 219 (1947). Note that the symbol δ is generally used to mean what is here called δ/β.

isovalent hyperconjugated structures $H_2\dot{C}=C=H_2$ (π_x hyperconjugation) and $H_2=C=\dot{C}H_2$ (π_y hyperconjugation).

For planar $C_2H_4^+$ the VB structure may be represented as $H_2=C^{+\frac{1}{2}}=C^{+\frac{1}{2}}=H_2$. For perp. $C_2H_4^+$, the electronic state would be ^2E of symmetry D_{2d}, for which there are two independent though equivalent orbital wave functions (twofold orbital degeneracy). For *one* of these (in the other, the · and + would be interchanged), the main VB structure $H_2=\dot{C}-C_+=H_2$ is in resonance with the homodatively isovalent hypercon-

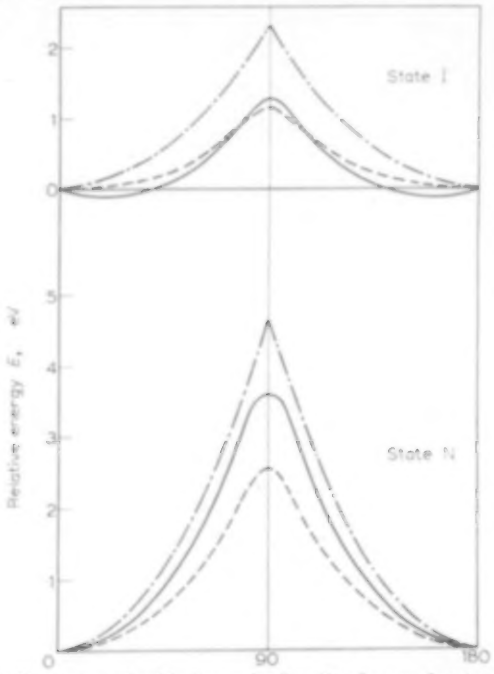


FIG. 2. Theoretically computed orbital energies (in eV) of ground states of C_2H_4 (state *N*, below) and $C_2H_4^+$ (state I, above) as functions of angle of twist ϕ. From unpublished work of Mulliken and Roothan (cf. reference 18). Full line curves are for best parameter values used ($\beta^* = 2\beta$, $\delta = 0$, $\beta = -3$ eV; dot–dash curves are for the case of *no hyperconjugation*; dashed curves for $\beta^* = 1.5\beta$, $\delta = \beta$, $\beta = -3$ eV.

jugated structure $H_2\dot{C}=C=C-H_2$ and with the neutrally isovalent structure $H_2=C=C-H_2$. (Note that these three structures correspond to those of perp. C_2H_4 if one replaces one · by a + in each.)

Fig. 2 shows the computed curves that we obtained for C_2H_4 and $C_2H_4^+$, but did not publish in 1947, for each of three choices of semiempirical parameters:[17] (a) no hyperconjugation ($\beta^* \rangle\rangle\rangle \beta$); (b) $\beta^* = 1{\cdot}5\beta$, $\delta = \beta$; (c) $\beta^* = 2\beta$, $\delta = 0$. Of these, the third choice is the most nearly correct according to recent views (β^*/β measures the degree of reluctance of an H_2 to give up its quasi-π bond in favor of a C=C bond, while δ measures the tendency of H_2 to release an electron to carbon; values of β^*/β of 2·0 and of δ about $-0{\cdot}3\beta$ to $-0{\cdot}5\beta$, corresponding to electropositive behavior of the H_2 group, have been currently accepted.[5]) Our curve for case (c) shows about 20 kcal stabilization by isovalent hyperconjugation in case (c); with $\delta/\beta < 0$, this would be somewhat increased.

For $C_2H_4^+$, allowance should have been made, as in later papers,[1, 12] for an additional parameter to take account of the increase in electronegativity of positively charged atoms, but it is probable that this and $\delta/\beta < 0$ would give for $C_2H_4^+$ an energy-angle curve of the same qualitative character as in case (c) but with intensified departure from cases (a) and (b). It will be noted that curves (a) and (b) have a flat minimum at $\phi = 0°$ corresponding to stability of planar $C_2H_4^+$, while case (c)—evidently as a result of incipient isovalent hyperconjugation—shows a low maximum at $\phi = 0°$ and shallow minima at perhaps about $\phi = 30°$; but still a fairly high barrier at $\phi = 90°$. This partial twisting may be understood by considering the following pair of VB structures for planar $C_2H_4^+$: $H_2\text{–}C\doteq C\overset{+}{=}H_2$ and $H_2\overset{+}{=}C\doteq C\text{–}H_2$. As long as $C_2H_4^+$ remains planar, these *cannot mix* with the main VB ground state structure given above, because they belong to excited states with wave functions sharply different in symmetry from the latter. But if twisting occurs, the symmetry distinctions are relaxed, and they can begin to mix in. (It may be remarked that description and understanding are easier using LCAO-MO theory.)[17]

It is now of great interest that experimental vacuum-ultraviolet spectroscopic data[18] on Rydberg states of C_2H_4 and C_2D_4 (which are essentially states of the ethylene positive ion plus an electron in an orbital so large that it has scarcely any influence on the molecular geometry) show unusual features which seem to be impossible to reconcile with a planar structure for $C_2H_4^+$, but which seem to be just about what might be expected for an energy-angle curve like the computed one for case (c) in Fig. 2. While an alternative interpretation of the spectroscopic data, involving excitation of a low-frequency out-of-plane bending instead of twisting frequency in the upper state, cannot be excluded with certainty, it seems much less probable. However, it is planned to make further experimental studies as soon as feasible which it is hoped may settle this question definitely, since there seems to be here an important probable confirmation of predicted effects of hyperconjugation.

III. SACRIFICIAL (ORDINARY) CONJUGATION AND HYPERCONJUGATION

(a) *General discussion*

Ordinary conjugation and hyperconjugation are *sacrificial*, in the sense that π-electron resonance stabilization is effected only by structures in which, as compared with the single dominant VB structure, one π bond has been lost. In the following discussion in this Section the qualifying adjective "ordinary" or "sacrificial" will usually be assumed to be understood when "conjugation" or "hyperconjugation" is used.

In the familiar example of 1,3-butadiene, with the dominant structure $H_2C{=}CH\text{–}CH{=}CH_2$, there are three minor structures which may collectively be symbolized by $H_2\overset{\circ}{C}\text{–}CH{=}CH\text{–}\overset{\circ}{C}H_2$. The two $\circ$ here represent either two $\cdot$ (odd electrons, between which there is a "long bond"), or $+$ and $-$, or $-$ and $+$ (two equivalent ionic structures of opposite polarity).

[18] P. G. Wilkinson and R. S. Mulliken, *J. Chem. Phys.* **23**, 1895 (1955); P. G. Wilkinson, *Canad. J. Phys.* **34**, 643 (1956). Stretching of the molecule in the ionized state also occurs; the twisting effect is approximately independent of this according to the spectroscopic data. When these papers were written the present Fig. 2, buried in the files, had been forgotten. In the first of these papers, an effort was made to explain the Rydberg spectra using a planar model with a very flat minimum for $C_2H_4^+$. However, as time went on, we felt more and more convinced that the data pointed to a twisted model. Finally, only recently, the earlier calculated curves here reproduced as Fig. 2, were rediscovered.

Very likely (although this point seems usually not to be recognized) the two ionic structures are much less important than the long-bond structure, since much more energy would be needed to create them. One should also especially note that this pair of structures involves *two-way* π dative action, as contrasted with the one-way π dative action involved in the subordinate VB structures in dative isoconjugation.

[*Note added 20 November* 1958. Recent calculations on butadiene by Berry[19] based on LCAO-MO wave functions throw light on this question. He finds that the VB structures $C{=}C{-}C{=}C$, $\dot{C}{-}C{=}C{-}\dot{C}$, and $\overset{\pm}{C}{-}C{=}C{-}\overset{\mp}{C}$ make up roughly 35, 5, and 0·6 per cent of the wave function, while simple ionic structures $C{=}C{-}C^{\pm}{-}C^{\mp}$ and $C^{\pm}{-}C^{\mp}{-}C{=}C$ make up 29 per cent and dispersion-type structures[20] $C^{+}{-}C^{-}{-}C^{+}{-}C^{-}$ and $C^{-}{-}C^{+}{-}C^{-}{-}C^{+}$ 30 per cent. These figures substantiate the unimportance of $C^{\pm}{-}C{=}C{-}C^{\mp}$, but indicate that other ionic structures may be more important even than $C{-}C^{\cdot}{=}C{-}\dot{C}$ in contributing to the π-electron resonance energy in conjugation. It seems likely that analogous ionic structures are important in all forms of conjugation and of hyperconjugation, both sacrificial and isovalent.]

Conjugation in diacetylene, according to π-electron theory, is entirely analogous to that in butadiene, except that it is *two-dimensional* instead of one-dimensional: predominant structure $HC{\fallingdotseq}C{-}C{\fallingdotseq}CH$, secondary structures $HC^{\cdot}{=}C{\doteq}C{=}\overset{\bullet}{C}H$, $HC_{\bullet}{\doteq}C{=}C{=}_{\bullet}CH$, and (very minor) $H\overset{\bullet}{C}_{\bullet}{-}C{\fallingdotseq}C{-}\overset{\bullet}{C}_{\bullet}H$.

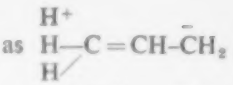
Examples of a structural situation which on the basis of quantum theory should also be described as conjugation occur in the cumulenes, for example one-dimensional conjugation for $H_2C{\doteq}C{=}C{\doteq}CH_2$ with secondary structures $H_2\overset{\bullet}{C}{-}C{\fallingdotseq}C{-}\overset{\bullet}{C}H_2$ and two-dimensional conjugation for $H_2C{\doteq}C{=}C{\doteq}C{=}CH_2$ with secondary structures $H_2\overset{\bullet}{C}{-}C{\fallingdotseq}C{-}\overset{\bullet}{C}{=}CH_2$ and $H_2C{\doteq}\underset{\bullet}{C}{-}C{\fallingdotseq}C{-}\underset{\bullet}{C}H_2$.

Ordinary *first-order hyperconjugation* is similar to ordinary conjugation in that there is one principal VB structure, and one bond is lost in the subordinate structures. It differs, however, in that the lost bond is a $[\pi]$ instead of a π bond. For example, in propylene (one-dimensional hyperconjugation) with main structure $H_3{\fallingdotseq}C{-}CH{\doteq}CH_2$, the subordinate structures are $H_3^{\circ}{=}C{\doteq}CH{-}\overset{\bullet}{C}H_2$. In methylacetylene (two-dimensional hyperconjugation) with main structure $H_3{\fallingdotseq}C{-}C{\fallingdotseq}CH$, the major subordinate structures are $H_3^{\circ}{=}C{\doteq}C{=}\overset{\bullet}{C}H$ and $H_{\bullet}{\fallingdotseq}C{=}C{\doteq}\underset{\bullet}{C}H$. Another example of two-dimensional hyperconjugation is found in allene, with main structure $H_2{=}C{\doteq}C{=}C{\doteq}H_2$ and secondary structures $H_2^{\circ}{-}C{\fallingdotseq}C{-}\overset{\bullet}{C}{\doteq}H_2$ and $H_2{=}\underset{\bullet}{C}{-}C{\fallingdotseq}C{-}\underset{\bullet}{H}_2$. Here the term hyperconjugation is used to describe a situation analogous to conjugation in the cumulenes.

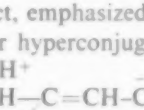
First-order hyperconjugation, like conjugation in butadiene and diacetylene, involves *two-way* dative action in the ionic subordinate VB structures. However, this may be slightly polar, in the sense that, for example in propylene, the structures $H_3^{+}{=}C{\doteq}CH{-}C^{-}H_2$ may be a little more prominent than $H_3{=}C{\doteq}CH{-}C^{+}H_2$, leading to a slight over-all polarity and dipole moment. But there is no theoretical justification for assuming that *only* the former of these two structures is important. In fact it is by no means clear theoretically that *either* of the two ionic structures should be comparable in importance with the long-bond structure $H_3^{\bullet}{=}C{\doteq}CH{-}\overset{\bullet}{C}H_2$. It seems

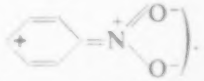
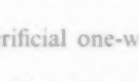
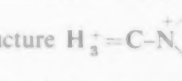
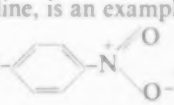
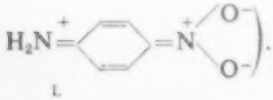
[19] R. S. Berry, *J. Chem. Phys.* (1959); based on wave functions obtained by him previously [*J. Chem. Phys.* **26**, 1060, (1957)]. For certain rather esoteric qualifications on the meaning of the percentages quoted, reference must be made to his new article.

[20] W. T. Simpson, *J. Amer. Chem. Soc.* **73**, 5363 (1951); *Ibid.* **77**, 6164 (1955).

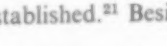
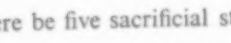
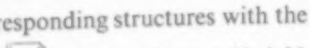
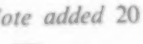
to the writer that the customary use of a symbolism such as  and corresponding emphasis on electron release, without any mention of an oppositely polarized ionic structure and, especially, of the long-bond structure, may be seriously misleading.

[*Note added* 20 *November* 1958. Berry's calculations on butadiene lend strong support, by analogy, to these remarks. At the same time the probable importance of dispersion-type ionic structures offers a reasonable mechanism for appreciable electron release, through mild predominance of $H_3^+\overline{=}C^- - C^+H - C^-H_2$ over $H_3^-\overline{=}C^+ - C^-H - C^+H_2$.]

In this connection, the fact, emphasized by Dewar, that the observed dipole moments in propylene and other hyperconjugated molecules can be explained without assuming such structures as  to be of appreciable importance, is significant. It seems then entirely possible that *both* the above-indicated ionic structures are of minor importance in typical cases of ordinary hyperconjugation. This, however, would not necessarily imply that the *long-bond* structure is also unimportant, nor that ionic structures are *always* unimportant in hyperconjugation. [*Note added* 20 *November* 1958. It seems likely that π-electron resonance may contribute appreciably to the dipole moment through a mild preponderance of $H_3^+ = C^- - C^+ - C^-$ over $H_3^- = C^+ - C^- - C^+$. (The structures $H_3^+ = C^- - C = C$ and $H_3^- = C^+ - C = C$ with the former preponderant need not be considered here, since they would also be present in the CH_3 group in the absence of π-electron hyperconjugation resonance.)]

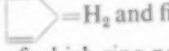
Before going further, an important difference between isovalent and sacrificial conjugation and hyperconjugation should be emphasized: while in the isovalent cases three important subclasses (dative, non-dative, and homodative) need to be distinguished, in the sacrificial case most examples (including all those thus far discussed) belong to the non-dative (or two-way dative) subclass. However, there is also a dative sacrificial subclass, whose most familiar examples are the nitro-compounds, for example nitrobenzene (four isovalent main structures such as with four π_z bonds, and three sacrificial one-way dative structures such as ). Nitroethylene, nitroacetylene, and the like, would belong to the same subclass. Similarly, nitromethane is an example of dative sacrificial hyperconjugation (main structure  , sacrificial one-way dative structure ). On the other hand, *p*-nitroaniline, like aniline, is an example of dative isovalent conjugation (main structures such as  , isovalent dative structure ).

in stabilizing respectively the allyl and methyl derivatives of aldehydes and ketones.

In fulvene, the presence of polar conjugation to an extent sufficient to create a dipole moment of about 1·2 D, and in the theoretically expected direction, seems to have been definitely established.[21] Besides the predominant VB structure  , there should here be five sacrificial structures, for example  , together with five corresponding structures with the charges reversed, and four long-bond structures such as  . [*Note added* 20 *November* 1958. Again, dispersion-type ionic structures, for example,  , are doubtless important.]

This case differs in an important way from that of butadiene or acrylaldehyde in which there is only *one* structure of each type ($-+$ $+-$, and $\cdot\cdot$). Namely, isovalent resonance (homodative, moreover, in the cases of the ionic structures) can occur *within* each group of sacrificial structures, causing pronounced extra stabilization. Under these circumstances, one may reasonably expect conjugation to have much more important effects than in butadiene or acrylaldehyde. But further, in view of the special, benzene-like, stability of the *cyclo*pentadienyl anion, it is reasonable to expect the ring-negative structures to predominate over the others. This result is confirmed theoretically by LCAO-MO computations and experimentally by the observed dipole moment.[21]

Similar results and conclusions have been found[21] for azulene. Here there is a *large number* of sacrificial conjugated structures, resonance among which should make conjugation important here. Further, the known benzene-like stability of the *cyclo*pentadienyl anion and the tropylium cation lead one to expect an over-all negative charge on the five-ring and positive charge on the seven-ring, and a dipole moment of corresponding polarity. The observed dipole moment is 1·0 D, which (although its sign has not been demonstrated experimentally) seems to be in reasonable agreement with the results of LCAO-MO computations.[21]

*cyclo*Pentadiene is the hyperconjugative analogue of fulvene, with a main structure  and five sets of sacrificially hyperconjugated VB structuressuch as , of which ring-negative members may be expected to predominate for the same reason as in fulvene.[22]

IV. HYPERCONJUGATION IN POSITIVE MOLECULE-IONS

Particularly in mass spectroscopy, there is increasing interest in the structure of positive ions. In even-electron ions (radical ions), homodative isovalent conjugation or hyperconjugation appears to have an important stabilizing effect [cf. Sections II(b) and II(d)]. In odd-electron ions (molecule ions) we encounter also homodative situations which are half-way between isovalent and sacrificial. Observed ionization

[21] G. W. Wheland and D. E. Mann, *J. Chem. Phys.* **17**, 264 (1949). The measurements were actually made on several derivatives, rather than on fulvene itself, but the reasoning back to fulvene seems convincing. Azulene: see also R. Pariser, *J. Chem. Phys.* **25**, 1112 (1956); W. G. Schneider, H. J. Bernstein and J. A. Pople, *J. Amer. Chem. Soc.* **80**, 3497 (1958).

[22] For results of LCAO-MO calculations, cf. G. Berthier and B. Pullman, *Bull. Soc. Chim. Fr.* **15**, 788 (1948); B. Pullman and A. Pullman, *Les Theories Electroniques de la Chimie Organique*. Masson et Cie, Paris (1952).

In non-dative sacrificial conjugation and hyperconjugation, one may of course distinguish between non-polar and polar cases (i.e., symmetrical or unsymmetrical two-way dative action), but the distinction is one of degree rather than kind. For example, conjugation in butadiene is necessarily non-polar, by symmetry, while first-order hyperconjugation in propylene must be polar, though perhaps only slightly so.

At this point something should be said about ordinary *second-order hyperconjugation*. This is now believed[5] to be a very small effect, and because of its universality it is difficult or impossible to isolate experimentally, but there seems to be no adequate reason to dismiss it as entirely negligible. Typical examples are found in ethylene (principal VB structure $H_2\overline{\overline{\pi}}C\overline{=}C\overline{\overline{\pi}}H_2$, hyperconjugative structures $\overset{\circ}{H}_2\text{–}C\overline{\overline{\pi}}C\overline{=}\overset{\circ}{H}_2$) and ethane (principal structure $H_3\overline{=}C\text{–}C\overline{=}H_3$, main hyperconjugative structures $H_3^{\circ}\overline{\overline{\pi}}C\overline{=}C\overline{\overline{\pi}}\overset{\circ}{H}_3$ and $\overset{\circ}{H}_3\overline{=}C\overline{\overline{\pi}}C\overline{=}\overset{\circ}{H}_3$). It will be noticed that second-order hyperconjugation is one-dimensional in ethylene, two-dimensional in ethane; also that is non-polar in both cases.

Characteristic of second-order hyperconjugation as described by VB structures is the fact that *two* [π] bonds are sacrificed, while one π bond is gained. There is, however, a net loss of one (π or [π]) bond just as in ordinary conjugation or first-order hyperconjugation; but it should be noted that this occurs in a way which differs from hyperconjugation in the same way that hyperconjugation differs from conjugation, so that the effect might well be called *hyper-hyperconjugation*.

An example in which the LCAO-MO treatment of second-order hyperconjugation differs considerably from the usual VB treatment is found in the ethyl ion.[1] Here (in addition to isovalent hyperconjugation) we have second-order hyperconjugation involving in the VB method just the main structure $H_3\overline{=}C\text{–}C^+\overline{\overline{\pi}}H_2$ and the subordinate structures $\overset{\circ}{H}_3\overline{=}C\overline{\overline{\pi}}C^+\text{–}\overset{\circ}{H}_2$. The LCAO-MO treatment[1] (provided suitable electronegativity-difference parameters are introduced) automatically includes also an important amount of the structure $H_3\overline{=}C\text{–}\overset{+}{\underset{-}{C}}\text{–}H_2$ in which the right-hand carbon atom as a whole is neutral. From the VB standpoint, the inclusion of this structure would be called an inductive effect. This is a rather extreme example of a characteristic feature of the LCAO-MO method which automatically includes any inductive effects which may occur in the π-electron system (σ-electron inductive effects—cf. Section II(a)—are of course not included).

(b) *Polar effects in conjugation and hyperconjugation*

As has been emphasized in Section III(a), the ionic secondary structures in ordinary "non-dative" conjugation and hyperconjugation occur in pairs of opposite polarity. The result may be non-polar, but if the atoms or groups between which, in these ionic structures, charge transfer takes place, differ in electronegativity, then some net polarity results. For conjugation, a simple example is $H_2C{=}CH\text{–}CH{=}O$, in which the secondary structure $H_2C^+\text{-}CH{=}CH\text{–}O^-$ obviously would predominate over $H_2C^-\text{–}CH{=}CH\text{–}O^+$. [*Note added* 20 *November* 1958. Probably much more important is predominance of $H_2C^+\text{–}C^-H\text{–}C^+H\text{–}O^-$ over $H_2C^-\text{–}C^+H\text{–}C^-H\text{–}O^+$.][2] For hyperconjugation, a similar example is $H_3{\equiv}C\text{–}CH{=}O$, where $H_3^+{=}C{=}CH\text{–}O^-$ must predominate over $H_3^-{=}C{=}CH\text{–}O^+$. [*Note added* 20 *November* 1958. Probably much more important is predominance of $H_3^+{=}C^-\text{–}C^+H\text{–}O^-$ over $H_3^-{=}C^+\text{–}C^-H\text{–}O^+$.] It seems possible that the polar effects in these cases may be of appreciable importance

potentials suggest that these ions also are rather strongly stabilized by conjugation and hyperconjugation.

The $C_2H_4^+$ ion has already been discussed in Section III(e). For planar $C_2H_4^+$, isovalent resonance between the two main structures $H_2C^+–\dot{C}H_2$ and $H_2\dot{C}–\overset{+}{C}H_2$, each a single-bonded structure, results in the equivalent of a half π bond. This may be summarized as $H_2C'\!=\!=C'H_2$, where C′ means $C^{+\frac{1}{2}}$.

The ionization potential of 1,3-butadiene is 1·45 V smaller than that of ethylene. This fact can be understood[23] in terms of much greater π_z-electron resonance stabilization by conjugation in the positive ion than in the neutral molecule. In the positive ion, the main VB structures may be described as $H_2C=CH–C'H\!=\!=C'H_2$ and $H_2C'\!=\!=C'H–CH=CH_2$ (that is, $H_2C=CH–C^+H–\dot{C}H_2$, $H_2C=CH–\dot{C}H–C^+H_2$ with resonance, and $H_2C^+–\dot{C}H–CH=CH_2$, $H_2\dot{C}–C^+H–CH=CH_2$ with resonance). Isovalent resonance between these is supplemented by resonance with the half-sacrificial structures $H_2\dot{C}–CH=CH–C^+H_2$ and $H_2C^+–CH=CH–\dot{C}H_2$, the over-all result being a much stronger conjugative effect than in the butadiene molecule. [*Note added* 20 *November* 1958. Probably dispersion-type structures such as $H_2C^+–C^-H–C^+H–\dot{C}H_2$ are also important.]

Homodative resonance within the π_z-electron system here distributes the positive charge fairly evenly over the carbon atoms, but a small amount of σ charge redistribution, by inductive effects in the σ bonds, must occur to alleviate in part an excess π_z positive charge on the two outer carbon atoms. Some further redistribution of charge by inductive electron release from the hydrogen atoms, via the C–H bonds, must of course also occur, and thereby contribute somewhat to the stabilization energy. But it seems likely that the major part of the stabilization energy is due to π_z-electron resonance.

In the positive ion of propylene, $C_3H_6^+$, with main structure $H_3\overset{\cdot\cdot}{=}C–C'H\overset{\cdot\cdot}{=}C'H_2$ one has homodative isovalent half-hyperconjugation with $H'_3\overset{\cdot\cdot}{=}C'–CH\overset{\cdot\cdot}{=}CH_2$ and homodative half-sacrificial hyperconjugation with $H_3^+\overset{\cdot\cdot}{=}C\overset{\cdot\cdot}{=}CH–\dot{C}H_2$ and $H''_3\overset{\cdot\cdot}{=}C\overset{\cdot\cdot}{=}CH–C^+H_2$ (altogether two main and four subordinate VB structures). The minimum ionization potential of propylene is 0·79 V lower than that of ethylene.[24] The difference may reasonably be ascribed largely to stabilization of the positive ion in consequence of methylation. (There is no reasonable doubt that it is a π_z electron which has been removed in the ground states of both the ethylene and the propylene ion.) Further, the stabilization energy can reasonably be identified in considerable part with homodative hyperconjugation energy, the situation being similar to that in the ethyl ion and in the toluenium ion [cf. Section III(d)]. However, electron release from the several hydrogen atoms by non-π_z (i.e. σ, [σ], and [π_y]) inductive effects must contribute very considerably to the stabilization energy (as also, though to a lesser extent, in the alkyl and methylated-benzene carbonium ions).

Observed further lowerings of ionization potential by further methylation or alkylation of ethylene[24] may be accounted for in the same way. A similar explanation can be given for the fact[24] that alkylation considerably lowers the ionization potentials of unsaturated and aromatic hydrocarbons in general.

[23] J. Fain and A. L. Matsen, *J. Chem. Phys.* **26**, 376 (1957).

[24] W. C. Price, *Chem. Rev.* **41**, 257 (1947) lists the ionization potentials of a large number of compounds and their alkyl derivatives (but see K. Watanabe, *J. Chem. Phys.* **26**, 542, 1773 (1957) for better values of some of the ionization potentials). He explains the lowering of ionization potentials by methylation in much the same way as here.

The alkyl derivatives of HCl, H_2O, H_2S, NH_3 and like molecules constitute another class of molecules in which substitution of alkyl groups for hydrogen atoms gives rise to lowered ionization potentials.[24] Here again, as in the alkylated aromatic and unsaturated compounds, hyperconjugation should help to stabilize the molecule ions. However, it is of a different and probably weaker type than in the unsaturated systems.

As examples, let us consider CH_3OH and CH_3Cl. In the ground electronic state of ionized CH_3OH, the main VB resonance structure is $H_3\equiv C\rightarrow \dot{\overset{+}{O}}H$. The most important subordinate structures are $H_3^{\bullet}=C=O^+H$ (involving isovalent hyperconjugation without charge transfer, i.e. *non-dative*) and $H'_3\!=\!C'\!-\!OH$ (involving homodative half-sacrificial half-hyperconjugation: i.e. half of one [π_x] bond is lost, but homodative transfer of positive charge from the O atom to the CH_3 group is accomplished). For CH_3Cl^+, the ground electronic state must be two-fold degenerate (^2E state), corresponding to removal of *either* a π_x or a π_y chlorine electron. The two substates are equivalent but independent; let us then consider just the one with a π_x electron removed. This is completely similar to CH_3OH^+: the main structure is $H_3\equiv C\rightarrow \dot{Cl}^+$ and the chief subordinate structures are $H_3=C=Cl^+$ and $H'_3\!=\!C'\!-\!Cl$.

It will be noted that *homodative isovalent* hyperconjugation, the strongest type of hyperconjugation, present in the ions of propylene and other alkylated aromatic or unsaturated compounds, is no longer present in CH_3OH^+, CH_3Cl^+, and the like. Hence it is reasonable to expect that non-π inductive effects may be more largely responsible for charge equalization and resulting stabilization in the latter than in the former. For the alkyl halides RCl, RBr, and RI, there is indeed strong spectroscopic evidence[25] indicating that hyperconjugation makes only relatively minor contributions to the structure of their positive ions; in other words, that the actual structure is not far from being $H_3\equiv C\rightarrow Cl^+$ alone.[26] However, it is generally believed that π bonding is weaker in higher-row than in first-row atoms, so that the conclusions derived from the spectroscopic evidence just cited may not apply with full force to $(CH_3F)^+$ and the ions of alkyl derivatives of H_2O and NH_3.

V. PLUVALENT CONJUGATION

Besides sacrificial and isovalent conjugation, there are a few cases in which conjugation occurs which may be described as *pluvalent* (one *more* bond in the secondary than in the main VB structure). Only *dative* pluvalent conjugation is to be expected. An example is BF_3 with main structure $F\leftarrow B\begin{matrix}\nearrow F\\ \searrow F\end{matrix}$ and three equivalent pluvalent structures of the type $F\!-\!\bar{B}\begin{matrix}\nearrow F^+\\ \searrow F\end{matrix}$. As is well known, resonance here causes strong stabilization.

[25] R. S. Mulliken, *Phys. Rev.* **61**, 277 (1942): see especially footnote 9 and Table II, second column.

[26] This would be in accord with views earlier expressed by the writer, in which (a), the relatively low ionization potentials for example of H_2O as compared with O and of HCl as compared with Cl, and (b), the still lower values for $(CH_3)_2O$, CH_3Cl, C_2H_5Cl, etc., were attributed to accumulation of negative charge on the O or Cl atom by transfer from the H atoms or alkyl group. [R. S. Mulliken *J. Chem. Phys.* **3**, 514 (1935)—but see K. Watanabe *J. Chem. Phys.* **26**, 542, 1773 (1957) for more reliable ionization potentials (which give a more consistent picture than the earlier values).]

Another example in which pluvalent conjugation may be of non-negligible importance is HF with main structure H–F and pluvalent conjugated structure $H^{-}\rightleftarrows F^{+}$. Similar structures may be of appreciable importance in hydrides in general,[25] at least where the H atom has become distinctly positive, enabling it to some extent to hold an electron in the excited H^{-} state $1s\,2p\pi$.

VI. THE RELATIONS BETWEEN INDUCTIVE AND MESOMERIC EFFECTS

Inductive effects, and their interaction with mesomeric effects, have been referred to several times in the preceding Sections. Since the two effects cannot always be sharply separated, especially in hyperconjugation, and since confusion (more of language than of understanding) can and does arise, it seems desirable to survey the relations between them.

To begin with, it may be worth while to remind the reader that ordinary inductive effects correspond, in VB theory, to resonance between covalent and ionic structures. It will simplify the discussion if at first we ignore hyperconjugation with its quasi-σ and quasi-π bonds, and think only in terms of σ and π bonds (including both π_x and π_y in the case of triple bonds) in the usual sense. Both σ and π bonds can be polar, that is, can exhibit the inductive effect. From what is known of the polarizabilities of σ and π electrons, one expects the π bonds to be more strongly polar than the σ bonds, but both polarized in the same direction, in unconjugated polar double or triple bonds (example $\begin{matrix}H\\H\end{matrix}\!\!>\!C\rightleftarrows O$). Polarity is expected when the atoms connected by a multiple bond belong to different elements, or when, if they both belong to the same element, they differ in charge or (in the case of σ bonds) in degree of s–p hybridization. In conjugated systems, *provided* the conjugation is not dative or homodative, the inductive or polarity effect is not essentially different quantum-mechanically than in unconjugated systems such as for example, $H_2C\rightleftarrows CH\rightarrow C\rightleftarrows O$.

In dative and homodative isovalent conjugation, however, there is either a strong cooperative, or a strong joint, inductive-mesomeric effect [here see also Section II(a)]. In dative conjugation the dative charge shift in one direction in the π-electron system should be accompanied typically by an *oppositely* directed "inductive" shift in the σ bonds; through this cooperative action, a *larger* "mesomeric" π-electron charge shift should occur than would be possible without it. [Example: $H_2C\rightleftarrows C\!<\!\begin{matrix}F\\H\end{matrix}$ with subordinate structure $H_2C^{-}\rightarrow C\!<\!\begin{matrix}F^{+}\\H\end{matrix}$. Here, in terms of quantum-mechanical theory, the arrowheads are shorthand for a variety of ionic structures of which $H_2C{=}C^{+}\!<\!\begin{matrix}F^{-}\\H\end{matrix}$ is the most important. In total, the F atom gives a fraction of a π_x electron (dative conjugation), but receives a rather different, probably larger fraction of a σ electron (inductive effect).]

In homodative isoconjugation, the mesomeric effect already *intrinsically* involves

a considerable amount of π_x electron shifting, in such a way as to partially but by no means entirely even out the π_x charge distribution as compared with that in a single one of the isovalent structures. One may reasonably describe the result as a *joint* mesomeric-inductive effect. *Further* charge equalization can then take place by the ordinary inductive effect in the π and especially in the σ bonds. The polarity readjustments in the σ bonds may here be described as *cooperative* in the same sense as in dative conjugation, and just as in that case should make possible larger mesomeric effects than would occur otherwise.

In summary, both mesomeric and π-electron inductive effects are resonance effects according to VB theory. In ordinary semi-empirical LCAO-MO theory, both *resonance* parameters β and *inductive* parameters δ (and ω, if there are charged atoms[1])—or the equivalent of these if the self-consistent-field method is used (either in its original form or in the Pariser–Parr or the Pople modification)—are introduced at the outset. It is then in general scarcely feasible to say, except qualitatively, how much of the total computed effect is due to covalent resonance, how much to bond-polarities (inductive effect), and how much to a mutual interaction of the two.

Turning now to hyperconjugation, we first replace some sets of σ bonds by $[\sigma]$, $[\pi_x]$, and $[\pi_y]$ GO (group orbital) bonds [cf. Section I(b)]. This procedure represents a partial adoption of the LCAO-MO viewpoint, after which, however, we can then carry the discussion further using the VB method. This last has been done in the present classification of hyperconjugation into types and subtypes. The $[\pi_x]$ bonds are now treated in the same way as π_x bonds, and all that was said above about the inductive and mesomeric effects in conjugation becomes directly applicable also to hyperconjugation.

In all cases where the hyperconjugation is intrinsically *two-dimensional*, $[\pi_y]$ and $[\pi_x]$ hyperconjugation must be treated alike, and what has been said about $[\pi_x]$ hyperconjugation then applies equally to the $[\pi_y]$ bonds. But otherwise, it is a matter of choice as to whether one wishes to consider $[\pi_y]$ hyperconjugation. In particular, second-order hyperconjugation is a form of $[\pi_y]$ hyperconjugtaion which for many purposes can be ignored, since it must usually be a relatively small effect and since, because of its universal background presence, it probably does not lead to appreciable observable differences in molecular properties [cf. last paragraphs of Section III(a)].

However, the *LCAO-MO treatment* of second-order hyperconjugation, because it includes an inductive parameter, yields a considerable stabilization energy in cases where transfer of a π_y electron can reduce charge inequalities, as for example in the ethyl ion.[1] From the VB standpoint, however, this LCAO-computed stabilization energy is nearly all due to an inductive effect in the π_y–$[\pi_y]$ electron system [cf. last paragraph of Section III(a)].

As already noted, $C{\equiv}R_3$ and $C{=}R_2$ σ bonds are treated in hyperconjugation *in part* like π_x bonds and in part like π_y bonds (and in part like σ bonds). In one-dimensional hyperconjugation (π_x and $[\pi_x]$ only), what would be classed as inductive effects if hyperconjugation were ignored are now classed *in part* as mesomeric (or as mixed inductive-mesomeric) effects. In two-dimensional hyperconjugation, a similar statement applies in double measure. Thus in speaking of inductive and mesomeric effects in hyperconjugated systems, it is desirable to take special care as to just what is meant by these terms. Perhaps it would be better if less emphasis than is customary were placed on trying to distinguish and separate them.

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VII. HYPERCONJUGATION AND THE BAKER–NATHAN EFFECT

Baker and Nathan,[27] in first introducing the ideas which Baker identifies with hyperconjugation,[28] suggested that when a "methyl group is attached to a conjugated system, the duplet of electrons forming the C–H bond in this group are appreciably less 'localized' than are those in a similarly placed C–C bond," and referred to the effect as a "new mechanism of electron release" "which either cannot function or is greatly diminished in the higher alkyl groups." In later papers it was assumed to decrease from a maximum for Me to zero for *t*-Bu. They used it initially to explain data on the velocity of interaction, by a bimolecular (S_N2) mechanism, of various alkyl-substituted benzyl bromides with pyridine in dry acetone, where for a single *p*-alkyl substituent they found that the velocity decreased by small amounts in the order Me > Et > *i*-Pr > *t*-Bu > H. They then extended the application of the idea in various directions.

In their preceding paper,[29] they indicated a belief that the activated state in the bimolecular reaction with pyridine is one which involves incipient anionization of the bromine atom, and is therefore speeded by easier electron release from the *p*-alkyl (or other) substituent group (or groups) in the substituted benzyl bromide. *Complete* anionization of the bromine would create a benzyl carbonium ion in which *p*-alkyl substitution should give rise to homodative isovalent hyperconjugation (main structures $H_3{\equiv}C$–C$_6$H$_4$–$\overset{+}{C}H_2$ and three ring-positive structures; hyperconjugated structure $H_3^+{=}C{=}$C$_6$H$_4$$=CH_2$) closely similar to that in McCaulay's methylated-benzene carbonium ions [cf. Section II(d)].

The concept of hyperconjugation as defined by the present writer[30] referred to definite states of individual molecules, mainly ground states but also spectroscopically excited states; it was also obviously applicable to radicals and ions. In some of his later papers,[31] Baker adduced evidence that the Baker–Nathan order (Me > Et > *i*-Pr > *t*-Bu > H) holds for the ground as well as activated states of certain hyperconjugated systems. He concluded that, for example in *p*-alkyl benzaldehydes, in addition to stabilization of the main VB structure R_2C–C$_6$H$_4$–$CH{-}O^-$ by structures R_2C–C$_6$H$_4$–$\overset{+}{C}H{-}O^-$ (inductive effect, or polar character, of the C=O π bond) and R_2C–C$_6$H$_4$$=CH{-}O^-$ (ordinary or sacrificial conjugation in the present terminology), there is stabilization by R_2C^+–C$_6$H$_4$–CH=O (inductive effect or polar

[27] J. W. Baker and W. S. Nathan, *J. Chem. Soc.* 1844 (1935).
[28] J. W. Baker, *Hyperconjugation*. Oxford University Press (1952).
[29] J. W. Baker and W. S. Nathan, *J. Chem. Soc.* 1840 (1935).
[30a] R. S. Mulliken, *J. Chem. Phys.* **7**, 339 (1939); cf. reference 3 in this paper with regard to the suggestion of the word "hyperconjugation" by W. G. Brown. In this paper (end of p. 345) it was concluded "that hyperconjugation changes (most likely decreases) the energy of the normal state", but that "the change is probably considerably smaller than for the [spectroscopically] excited states". [30b] Regarding some previous history of the concept of hyperconjugation (before the name was suggested), going back to Wheland (1934), see R. S. Mulliken, C. A. Rieke and W. G. Brown *J. Amer. Chem. Soc.* **63**, 41 (1941). Regrettably, the papers of Baker and Nathan, and of Baker and other collaborators had not then come to our attention. [30c] A still earlier example, of what would here be called isovalent hyperconjugation, is contained in the writer's discussion of the theory of the structure of twisted ethylene in *Phys. Rev.* **43**, 279 (1933).
[31] J. W. Baker, *J. Chem. Soc.* 191 (1942); *Ibid.* 445 (1938); 796 (1941); *Hyperconjugation*. Oxford University Press (1952).

character in the σ bond from R_3C to the ring), and finally by $R_3{}^+C=\langle\bigcirc\rangle=CH-O^-$ (ordinary or sacrificial hyperconjugation in the present terminology) but with a maximum effect of this last structure for R = H and *no* effect for $R = CH_3$.

In two respects the quantum-mechanical theory of π-electron resonance in hyperconjugation seems to deviate strongly from the ideas presented by Baker.

(1) The theory gives no indication that the hyperconjugative π-electron resonance power of a group $\begin{matrix}R\\ R'\\ R''\end{matrix}\!\!\diagdown\!\!\!-C$ should depend in an essential way on how many of R, R′, and R″ are H atoms. Qualitatively, bonds from H atoms, Me or other alkyl groups or indeed from any atom or group should be alike capable of participating in hyperconjugative resonance. Quantitative differences would be expected, of course; a C–C bond from Me might be less (or more) effective than a C–H bond from H,[32] but it would not be expected to be negligibly effective, nor is there any obvious reason why it should be radically different in effectiveness. This statement applies both to ordinary and to isovalent hyperconjugation.

In any event, the Baker–Nathan effect, in so far as it pertains to differences between C–H and C–C hyperconjugation, should not itself be called hyperconjugation, although it might be called *differential* hyperconjugation (for C–C relative to C–H).

Taft's Conference paper includes a thorough discussion of evidence of various kinds that π-electron resonance occurs for C–C as well as for C–H hyperconjugation although (in accord with the Baker–Nathan effect) more strongly for the latter. The evidence pertains both to ground state hyperconjugation and to activated state hyperconjugation (reaction rates, etc.).

(2) The theory [see detailed discussion of butadiene and propylene in Section III(a)] does not indicate that ordinary hyperconjugation should in general be an important electron-release mechanism (nor that, if it were, H should be better than Me—rather the contrary).

[*Note added* 20 *November* 1958. The probable importance of dispersion-type ionic states now furnishes a reasonable theoretical basis for appreciable electron release in hyperconjugation; and perhaps also for greater release in C–H than in C–C hyperconjugation, since H is more electropositive than C, and therefore $H_3{\equiv}$ or $H_2{=}$ than e.g. $(\diagdown\!\!-C)_3{\equiv}$ or $(\diagdown\!\!-C)_2{=}$.] *Maximum strength* of hyperconjugative effects, including electron release, should occur in homodative isovalent hyperconjugation, as for example in McCaulay's alkylated aromatic carbonium ions [cf. Section II(d)].

In so far as the Baker–Nathan effect is concerned with activated states in chemical reactions, it is more difficult to say what might be expected theoretically than when one is concerned only with molecules or ions in ground (or definite spectroscopically excited) states. Presumably activated states are more affected by steric factors than ground states. Solvent effects can of course be important for any state, particularly for an ionic or highly polar state. However, when activated states involve incipient

[32] R. S. Mulliken and R. G. Parr, *J. Chem. Phys.* **19**, 1271 (1951). Equation (23a) and footnote 26 of this paper attributed variations in heats of formation of variously branched hydrocarbons to *greater* C–C than C–H second-order hyperconjugation energies. However, especially in view of the theoretically expected smallness of all second-order hyperconjugation effects,[5] their attribution must be considered speculative.

carbonium ion formation, they should presumably involve incipient homodative isovalent hyperconjugation. Taft's Conference paper indicates that the relative importance of C–H and C–C hyperconjugation is similar in activated and ground states.

In connection with the role of hyperconjugation in reaction mechanisms, a survey by Wheland[33] of the explanation of the Markovnikov rule for the addition of reagents of type HX to a double bond is of interest. It is assumed that the reaction proceeds through a (perhaps only incipient) carbonium-ion-salt activated complex. The explanation is then essentially that, taking propylene as the simplest example, the isopropyl ion, with main structure $H_3{\cong}C{-}CH{-}C{\cong}H_3$, is stabilized by *two* (homodative isovalent) hyperconjugated structures ($H_3{\cong}C{-}CH{=}C{=}H^+$ and $H^+{=}C{=}CH{-}C{\cong}H_3$), whereas the propyl ion $H_3{\cong}C{-}C{-}C^+{=}H_2$ is stabilized only

by one ($H_3{\cong}C{-}C{=}C{=}H_2$). Hence the *iso*propyl-type complex is more stable and

the addition takes place accordingly. Mass spectroscopy as well as hyperconjugation theory furnishes evidence for the greater stability of the *iso*propyl than of the propyl ion; however, there are also questions of the geometry of the actual ions, but it would lead too far to attempt to discuss these questions further here.

[33] G. W. Wheland, *Resonance in Organic Chemistry*, pp. 430 *et seq.* Wiley, New York (1955); C. K. Ingold, *Structure and Mechanism in Organic Chemistry*. Cornell University Press, Ithaca (1953).

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THE CHEMISTRY OF MOULD METABOLITES—III*

STRUCTURE OF CINNABARIN (POLYSTICTIN)†

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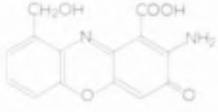
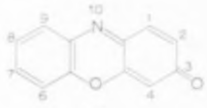
Abstract—Cinnabarin (polystictin) is shown to be 1-carboxy-2-amino-9-hydroxymethylphenoxazin-3-one. Previous degradative and spectroscopic studies on cinnabarin and its derivatives are interpreted on the basis of this structure, which is confirmed by the transformation of methyl cinnabarin into the known 1:9-dimethoxycarbonyl-2-aminophenoxazin-3-one.

FOLLOWING upon the isolation of the red pigment, cinnabarin (polystictin), from the wood-rotting fungi, *Coriolus sanguineus*[1,2] and *Trametes cinnabarina*,[3] various degradative studies have been reported.[4,5,6,7] In a preliminary communication,[8] structure (I) was proposed for this mould metabolite and it is now intended to detail the evidence that has led to this formulation.

The acidic character of cinnabarin, $C_{14}H_{10}O_5N_2$, which is converted into methyl cinnabarin by the action of diazomethane, or by methyl iodide and potassium carbonate in acetone,[2] is attributed to a carboxyl group. On mild treatment with methanolic potassium hydroxide solution cinnabarin yields the non-acidic decarboxycinnabarin,[1] and as the elimination of the elements of carbon dioxide is achieved without significant change in the characteristic absorption spectrum,[5] the reaction is represented as a simple decarboxylation. In addition, cinnabarin contains a hydroxyl group which is acetylated by the action of acetic anhydride–sulphuric acid.[2] Similarly methyl cinnabarin yields methyl O-acetylcinnabarin, by the action of acetic anhydride–pryidine.‡,[5]



(I)



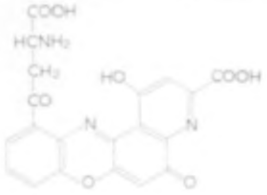
(II)

Now, the nature of the nucleus has been established by the isolation of phenoxazin-3-one (II), on fusion of cinnabarin with zinc dust,[4,5] and this mould metabolite is

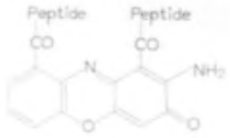
* Part II, G. W. K. Cavill, P. S. Clezy and J. R. Tetaz, *J. Chem. Soc.* 2646 (1957).
† For preliminary communication, see *Proc. Chem. Soc.* 346 (1957).
‡ Methyl O-acetylcinnabarin was originally described[5] as an N-acetyl derivative, cf. Gripenberg.[6]

[1] Report *Nat. Health Med. Res. Council Australia* p. 12 (1946); R. Lemberg, *Aust. J. Exp. Biol. Med. Sci.* **30**, 271 (1952).
[2] G. W. K. Cavill, B. J. Ralph, J. R. Tetaz and R. L. Werner, *J. Chem. Soc.* 525 (1953).
[3] J. Gripenberg, *Acta Chem. Scand.* **5**, 590 (1951).
[4] G. W. K. Cavill and J. R. Tetaz, *Chem. & Ind.* 986 (1956).
[5] G. W. K. Cavill, P. S. Clezy and J. R. Tetaz, *J. Chem. Soc.* 2646 (1957).
[6] J. Gripenberg, E. Honkanen and O. Patoharju, *Acta Chem. Scand.* **11**, 1485 (1957).
[7] J. Gripenberg, *Proc. Chem. Soc.* 233 (1957).
[8] G. W. K. Cavill, P. S. Clezy and J. R. Tetaz, *Proc. Chem. Soc.* 346 (1957).

thus grouped with the ommochromes, for example xanthommatin[9] (III), and with the actinomycins[10,11] (IV), as a new class of organic pigments in Nature. The latter compounds contain a nitrogen atom in the 2-position, and considerable support for a 2-aminophenoxazin-3-one chromophore in cinnabarin is provided by a comparison of the light absorption data of cinnabarin and its derivatives with that of various natural and synthetic 2-aminophenoxazin-3-ones.[5] For example, the spectrum of



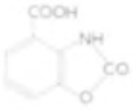
(III)



(IV)

decarboxycinnabarin (max at 237 and 421, 437 mμ; log ε 4·15 and 4·10, 4·12) is almost identical with that of 2-aminophenoxazin-3-one (max at 237 and 421–436 mμ; log ε 4·17 and 4·10).

The isolation of benzoxazolone-4-carboxylic acid (V), on oxidation of cinnabarin with potassium permanganate,[6] may be compared with the known conversion of 2-aminophenoxazin-3-one into benzoxazolone, and of actinomycin (IV) into 7-methylbenzoxazolone-4-carboxylic acid,[12] thus confirming the phenoxazone nucleus. In addition, the isolation of this C_7 moiety, a degradation product of the benzenoid ring, establishes the presence of a carbon substituent at position 9 of the phenoxazone nucleus.[6] Now (V) has been obtained by the oxidation of cinnabarin with potassium permanganate, but not by the action of alkaline hydrogen peroxide, hence the carboxyl group results from further oxidation of the original substituent in position 9.[6] As cinnabarin contains a 2-aminophenoxazin-3-one chromophore, and possesses a carboxyl group, the above substituent must be a hydroxymethyl group (cf. I).



(V)

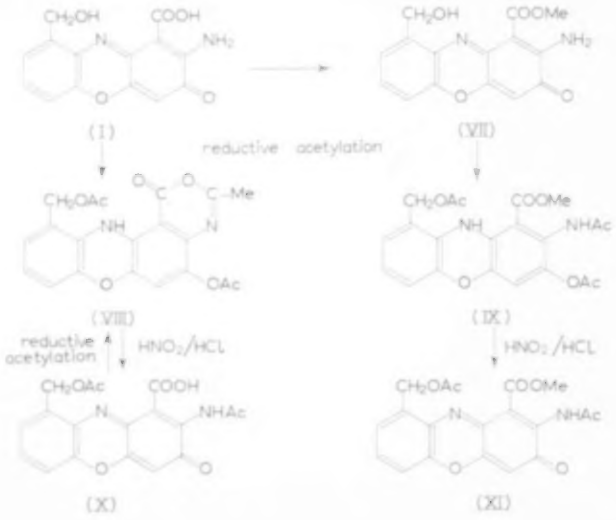
(VI)

The action of aqueous alkali on cinnabarin has resulted in the ready liberation of one molar proportion of ammonia[1,2,3] and corresponds to a hydrolysis of the 2-amino group. More recently a milder hydrolysis of cinnabarin, with aqueous sodium hydroxide solution, has given a quinone, $C_7H_7O_5N$, which is further hydrolysed to 2:5-dihydroxy-*p*-benzoquinone, carbon dioxide and ammonia.[7] Such a C_7 moiety must correspond to the quinonoid ring of the aminophenoxazone nucleus, and thus, is represented as a 2-amino-5-hydroxy-*p*-benzoquinone carboxylic acid, presumably (VI). The carboxyl group is that originally present in cinnabarin. The alternative

[9] A. Butenandt, U. Schiedt and E. Bickert *Liebigs Ann.* **588,** 106 (1954); A. Butenandt, U. Schiedt, E. Bickert and R. J. T. Cromartie, *Ibid.* **590,** 75 (1955).
[10] H. Brockmann and H. Muxfeldt, *Angew. Chem.* **68,** 69 (1956).
[11] S. J. Angyal, E. Bullock, W. G. Hanger, W. C. Howell and A. W. Johnson, *J. Chem. Soc.* 1592 (1957).
[12] E. Bullock and A. W. Johnson, *J. Chem. Soc.* 1602 (1957).

formulation[7] of this compound as a 2:5-dihydroxy-*p*-benzoquinone carboxamide is untenable for cinnabarin does not contain an amide group.[5] Rather the oxamic acid, acid, obtained on treatment of cinnabarin with alkaline hydrogen peroxide solution,[6] results from the same hydrolytic fission of the quinonoid ring as yields pyruvic acid, oxalic acid, carbon dioxide and ammonia.*,[5]

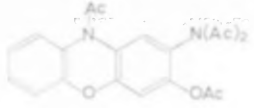
Evidence for the *ortho*- relationship of the 1-carboxy and 2-amino substituents on the quinonoid ring is provided by a re-interpretation of the experimental data[2,5] on the reductive acetylation of cinnabarin and its derivatives (cf. Part II).[5] In the conversion of cinnabarin into triacetylanhydrodihydrocinnabarin (VIII), and of methyl cinnabarin (VII) into methyl triacetyldihydrocinnabarin (IX), three acetyl groups have been introduced into these products. As O-acetylcinnabarin and methyl O-acetylcinnabarin are also converted into the triacetyldihydro- derivatives (VIII) and (IX) respectively, one acetyl group is accommodated on the primary alcoholic group at C_9.[7] Methyl cinnabarin and methyl O-acetylcinnabarin do not form the anhydro compound, hence the hydroxyl group involved in this cyclisation must be that of the carboxylic acid, and the anhydro compound is then the oxazine (VIII) formed by a an *ortho*-hydroxyl (or potential hydroxyl) group with an adjacent acetylamino ring closure of the 1-carboxyl with the 2-acetylamino group. Previously cyclisation of substituent was considered,[5] but it is now shown that no oxazole formation results from the reductive acetylation of 2-aminophenoxazin-3-one. The third acetyl group, placed on the hydroxyl group now located in position 3, stabilises the reduced products (VIII) and (IX).



2-Aminophenoxazin-3-one, on similar treatment with zinc dust, acetic anhydride and a trace of pyridine, is converted into a tetra-acetyldihydro- compound formulated as (XII). Thus the triacetyldihydro- derivative (IX), from methyl cinnabarin, is

* The fact that cinnabarin shows a small acetyl value (approximately one third to one quarter of an acetyl group) and that the results of acetyl determinations on many of the derivatives of cinnabarin are high, is attributed to this hydrolytic fission.

comparable with a diacetyldihydro- derivative of the unsubstituted aminophenoxazone. Presumably additional acetylation of methyl cinnabarin* is prevented by the steric effects of the substituents in position 1 (—$COOCH_3$) and position 9 (—CH_2OCOCH_3). The structures of the reduced products (VIII) and (IX) are confirmed



(XII)

by their oxidation, with nitrous acid in dilute hydrochloric acid, to give the acidic O:N-diacetylcinnabarin (X, with the re-addition of the elements of water), and its methyl ester (XI), respectively. Only one acetyl group, that in position 3, is removed in each case and the infra-red data shows the loss of the appropriate carbonyl absorption ~1770 cm^{-1}. In addition the ultra-violet spectrum of methyl O:N-diacetylcinnabarin (XI) (max at 237 and 404 mμ; log ε 4·48 and 4·40) closely resembles that of 2-acetylaminophenoxazin-3-one (max at 241 and 404 mμ; log ε 4·56 and 4·45).

The infra-red spectrum of cinnabarin† and of O-acetylcinnabarin ("Nujol" mull) show no features in the 3 mμ region characteristic of a carboxylic acid, an observation that previously led us to attribute the acidity of the parent compound to a phenolic group.[2] However, a carboxyl group in position 1 may hydrogen bond with the ring nitrogen atom and with the 2-amino group, whence cinnabarin is represented as (Ia) (Flett[14] attributes poor absorption of the hydroxyl group in 3-amino-2-naphthoic acid to internal hydrogen bonding). The band at 3505 cm^{-1} in cinnabarin is then assigned to the alcoholic hydroxyl group and, in agreement, is absent from O-acetylcinnabarin Further the band at 1672 cm^{-1} in cinnabarin, and at 1691 cm^{-1} in O-acetylcinnabarin, is assigned to the carbonyl group of the carboxylic acid, whilst that at 1727 cm^{-1} in the latter compound is characteristic of the acetate ester. Methyl cinnabarin (VIIa), which showed absorption at 1656 cm^{-1} ("Nujol" mull),[2] exhibits bands at 1676 cm^{-1} and 1654 cm^{-1} in solution (carbon tetrachloride), and the higher frequency is assigned to the ester carbonyl group which is hydrogen bonded wih the 2-amino group, (cf. absorption of methyl N-methylanthranilate at 1685 cm^{-1} in carbon tetrachloride).[15] The lower frequency (1654 cm^{-1}) is that of the phenoxazin-3-one carbonyl group.[5,16] Methyl O-acetylcinnabarin exhibits comparable bands at 1675 cm^{-1} and 1655 cm^{-1}, and in agreement with Gripenberg,[6] the additional absorption at 1745 cm^{-1} is assigned to the acetate carbonyl group. The consistently low values recorded for the NH stretching modes of the amino group in cinnabarin[2] and in O-acetylcinnabarin,[2] and in methyl cinnabarin (3441 cm^{-1}, 3319 cm^{-1} in carbon tetrachloride) and in methyl O-acetylcinnabarin (3446 cm^{-1}, 3319 cm^{-1} in carbon tetrachloride), parallel the low values already noted for the carbonyl absorption of the acid or ester in these

* The compound, m.p. 176°, which has been isolated as a by-product of the reductive acetylation of methyl cinnabarin,[10] is probably a tetra-acetyldihdro- derivative.

† Infra-red absorption spectra ("Nujol" mull) for cinnabarin and its derivatives are recorded in Part I.[2] (An absorption at 1799 cm^{-1} originally reported[2] for triacetylanhydrodihydrocinnabarin (VIII) has not been duplicated and is attributed to an artifact).[13] Many of these compounds are insufficiently soluble for complete examination in solution (chloroform or carbon tetrachloride).

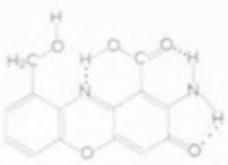
[13] J. R. Tetaz, Thesis, N.S.W. University of Technology (1955).

[14] M. St. C. Flett, *J. Chem. Soc.* 962 (1951).

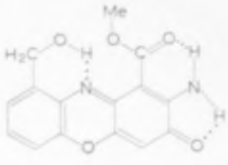
[15] R. S. Ramussen and R. R. Brattain, *J. Amer. Chem. Soc.* **71**, 1073 (1949).

[16] H. Musso and H. G. Matthies, *Chem. Ber.* **90**, 1814 (1957).

compounds, and further support the hydrogen bonded formulations (Ia and VIIa). In contrast, but in agreement with structure (XIII), decarboxycinnabarin which lacks the carboxyl group in position 1, exhibits higher NH stretching values (3514 cm^{-1}, 3392 cm^{-1} in chloroform). Suprisingly methyl cinnabarin and decarboxycinnabarin



(Ia)

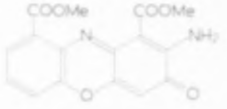


(VIIa)

show no absorption attributable to the alcoholic hydroxyl group; hence on esterification, or on elimination of the carboxyl group in position 1, the alcoholic group may hydrogen bond with the ring nitrogen atom (see VIIa and XIII). The orientation of the substituents—1-carboxy, 2-amino, and 9-hydroxymethyl—is thus strongly supported by the infrared spectroscopic data.

Confirmation of structure (I) for cinnabarin is provided by the transformation of methyl cinnabarin into the known 1:9-dimethoxycarbonyl-2-aminophenoxazin-3-one (XIV). As the oxidation has been achieved under mild conditions, employing successively manganese dioxide in chloroform, and chromium trioxide-sulphuric acid in acetone, direct evidence is provided for the presence of the hydroxymethyl substituent in position 9. The yield of the 9-carboxy-1-methoxycarbonyl-intermediate is small, much of the methyl cinnabarin being recovered, and the unexpected resistance to oxidation shown by this aromatic carbinol may be attributed to the "locked" position of the hydrogen atom of the hydroxyl group (see structure VIIa). Such strong intramolecular hydrogen bonding is an especial feature of cinnabarin and its derivatives.

(XIII)



(XIV)

EXPERIMENTAL

Melting points are uncorrected. Light petroleum has b.p. 60–80°. Neutralised alumina is prepared by washing Peter Spence (grade H) alumina with methanol–acetic acid (9 : 1), triturating it with hot methanol until all washings are neutral, and drying it at 150–200°. Carbon, hydrogen and nitrogen microanalyses are by Dr. E. Challen of this University, additional microanalyses by C.S.I.R.O. Microanalytical Laboratory (Melbourne), and infra-red spectra by Mr. I. Reece.

Decarboxycinnabarin.[1] Cinnabarin (100 mg) in methanolic potassium hydroxide solution (20 ml, 20%) was heated at 100° on the steam bath. After 3 min the dark red solution was cooled rapidly to room temp, acidified (2 N H_2SO_4), and extracted with chloroform (10 × 50 ml). The chloroform layer was washed (2% sodium

carbonate solution, then water), dried (anhydrous sodium sulphate), and on evaporation gave a red-brown product (40 mg). After repeated recrystallisation from chloroform, *decarboxycinnabarin* was isolated as dark red needles, m.p. >250° with decomposition. (Found: C, 64·1; H, 4·2; N, 11·4%. $C_{13}H_{10}O_3N_2$ requires: C, 64·5; H, 4·2; N, 11·6%).

Reductive acetylation of 2-aminophenoxazin-3-one. 2-Aminophenoxazin-3-one (0·70 g) in acetic anhydride (30 ml) and pyridine (1 ml) was heated under reflux with excess zinc dust for 10 min. The zinc was filtered off, and the pale yellow solution poured onto ice when a colourless solid slowly precipitated. This reductive acetylation *product* (0·70 g) was recrystallised from benzene-light petroleum, and finally obtained as colourless needles, m.p. 184–185°, from ethanol. (Found: C, 62·9; H, 4·7; N, 7·4; Ac, 44·7; $C_{20}H_{18}O_6N_2$ requires: C, 62·8; H, 4·8; N, 7·3; 4Ac, 45·0%). No evidence of oxazole formation was noted.

*Oxidation of methyl cinnabarin.** Methyl cinnabarin (30 mg) in chloroform (40 ml) was shaken for 72 hr with manganese dioxide (300 mg), prepared according to the method of Attenburrow *et al.*[17] The manganese dioxide was then filtered off and well washed with chloroform. The combined filtrates, on evaporation, yielded an orange product which was dissolved in acetone (120 ml), then the solution was treated (under nitrogen) with one drop of chromium thioxide-sulphuric acid reagent.[18] Excess of the oxidant was still present after 1 hr at room temp, when the mixture was poured into water. The product was extracted into chloroform and the acidic material separated by treatment with 1% sodium carbonate solution. The chloroform layer yielded methyl cinnabarin† (25 mg), m.p. 236–238° with decomposition, undepressed on admixture with the starting material. The acidic product, after re-extraction into chloroform, was treated with an excess of diazomethane in ether, and the crude orange ester so obtained was purified by chromatography on neutralised alumina, being eluted with benzene–chloroform (3 : 1). The product, 1:9-dimethoxycarbonyl-2-aminophenoxazin-3-one, was finally isolated as bright orange needles (2·0 mg), m.p. 224–226° with decomposition, undepressed on admixture with an authentic specimen.[11] The identity of the oxidation product with the synthetic specimen was confirmed by comparison of the spectra in the ultra-violet (acid, neutral and alkaline)[11] and in the infra-red region and by paper chromatography.‡‡

Acknowledgments—We thank Dr. R. Lemberg, F.R.S., for his interest and for facilities afforded one of us (P. S. C.), and Professor A. W. Johnson for a specimen of 1:9-dimethoxycarbonyl-2-aminophenoxazin-3-one. A National Health and Medical Research Council grant (to P. S. C.) is gratefully acknowledged.

* We are indebted to Mr. F. W. Whitfield for the paper chromatography of methyl cinnabarin, 1:9-dimethoxycarbonyl-2-aminophenoxazin-3-one and the oxidation product.

† R_f 0·59, in water–*n*-butanol–*iso*proponal–propionic acid (75 : 5 : 5 : 15), and R_f 0·56, in water–*n*-butanol–*iso*propanol–piperidine (75 : 5 : 5 : 15), in each case identical with that of the starting material.

‡ R_f 0·73, in water–*n*-butanol–*iso*propanol–propionic acid (75 : 5 : 5 : 15), and R_f 0·83, in water–*n*-butanol–*iso*propanol–piperidine (75 : 5 : 5 : 15).

[17] J. Attenburrow, A. F. B. Cameron, J. H. Chapman, R. M. Evans, B. A. Hems, A. B. A. Jansen and T. Walker, *J. Chem. Soc.* 1094 (1952).

[18] C. Djerassi, R. R. Engle and A. Bowers, *J. Org. Chem.* **21**, 1547 (1956).

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THE EFFECT OF A POSITIVE CHARGE ON A $\pi \rightarrow \pi^*$-TRANSITION

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(*Received* 30 *July* 1958)

Abstract—The position of the maximum for the $\pi \rightarrow \pi^*$-transition of a bicyclic ketone containing a quaternary nitrogen atom at 3·1 Å from an α:β-unsaturated ketone system is shown to depend largely upon electrostatic (repulsion) destabilization in both ground and excited states, the latter being affected more strongly.

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INTERPRETATIONS of ultraviolet absorption spectra have been of considerable value in the elucidation of structure and in the understanding of the electronic and steric effects of substituents on conjugated systems. One has only to remember the order introduced by the Woodward rules[1] into the prediction of the maxima of conjugated ketones and dienes to appreciate the value of reasonable empirical rules for such purposes. In extending the principle of the Woodward rules to other substituents, it is necessary to ensure that (1) the effects are large enough to be discussed, (2) the structural feature of concern is actually responsible for the absorption observed, and (3) the effect of the solvent can be discounted or calculated.

Georgian[2] has recently reported the interesting fact that a hetero-atom inserted at the 3-position of a bi*cyclo*[4.4.0] dec-6-en-8-one (I) causes a significant decrease in the position of the short wavelength maximum. The magnitude of the change was reportedly greater when the hetero-atom (**H**) carried a formal positive charge.

I

The values given by Georgian for 95% ethanol are listed in Table 1.

Iodide ions possess an intense absorption maximum at ca. 2195 Å in 95% ethanol.[3] The fact that iodide ion absorbs strongly in the region of the maxima given by Georgian for quaternary salts as well as the marked solvent-sensitivity of the maxima for α:β-unsaturated ketones[4] suggested that a more detailed examination of an appropriate salt* and of the solvent effect was necessary.

The absorption spectra of three compounds with the basic structure (I) were investigated in four different solvents. The compounds were bi*cyclo*[4.4.0] dec-5-en-4-one (II) (I, **H** = CH_2),[6,7] 3-methyl-3-azabi*cyclo*[4.4.0]dec-6-en-8-one (III) (I, **H** = N—CH_3)[8] and a quaternary salt derived from (III), (IV) (I, **H** = $N(CH_3)_2^+ClO_4^-$).

* Methiodide salts have been used by others[5] to obtain maxima of interest in connection with this problem.

[1] R. B. Woodward, *J. Amer. Chem. Soc.* **63**, 1123 (1941); **64**, 76 (1942).
[2] V. Georgian, *Chem. & Ind.* 930 (1954); 1480 (1957).
[3] E. M. Kosower, R. L. Martin and V. W. Meloche, *J. Chem. Phys.* **26**, 1353 (1957).
[4] E. M. Kosower, *J. Amer. Chem. Soc.* **80**, 3261 (1958).
[5] C. B. Clarke and A. R. Pinder, *J. Chem. Soc.* 1967 (1958).

TABLE 1. MAXIMA FOR VARIOUS COMPOUNDS OF STRUCTURE I

H	λ_{max} (Å)
$N{-}CH_3$	2320[a]
S	2300
SO_2	2290
$SCH_3{}^+I^-$	2220
$N(CH_3)_2{}^+I^-$	2210
(CH_2)[b]	(2400)[b]

[a] Identical with the value reported.[6] The value of 2275 Å has been given for *methanol*.[6]
[b] The value used by Georgian,[2] and supposedly calculated by the use of the Woodward rules.[1] Use of the rules as stated gives, however, the maximum as 2440 Å. Zeiss and Martin,[7] found a maximum at 2380 Å (presumably in 95% ethanol), in agreement with the results of W. T. Tsatsos, Ph.D. Thesis, University of Wisconsin, 1954.

The solvents used were chosen to give the widest possible range of solvent polarity.[9] The results are shown in Table 2.

In contrast to the value of 2210 Å reported by Georgian[2] for the quaternary iodide IV (I^- replacing ClO_4^-) we have found the maximum in 95% ethanol at 2290 Å. There can be little doubt, therefore, that a positive charge at position 3 in

TABLE 2. $\pi \rightarrow \pi^*$-TRANSITIONS

Solvent	Z[a]	Compound II λ_{max} (Å)	Compound II ε_{max}	Compound III λ_{max} (Å)	Compound III ε_{max}	Compound IV λ_{max} (Å)	Compound IV ε_{max}
Water	94·6	2455	(15,100)	2390	(13,700)	2330	(15,500)
95% Ethanol	80·8	2380	(15,400)	2325	(14,100)	2290	(15,600)
Acetonitrile	71·3	2345	(15,700)	2300	(14,100)	2260	(15,500)
*cyclo*Hexane	60·1[b]	2290	(16,500)	2255	(14,200)	—[c]	

[a] Solvent polarity values.[8]
[b] Taken as equal to 2:2:4-trimethylpentane (*iso*octane).
[c] Insoluble.

the bicyclic molecule (I), displaces the maximum in 95% ethanol to shorter wavelengths. It is, however, clear that the use of the iodide salts leads to an erroneously exaggerated figure for this displacement.[2,5] In addition, the size of the actual displacement (from II to IV) varies with the solvent, changing from 125 Å in water to 85 Å in acetonitrile. The effect of solvent is displayed more effectively by a plot

[6] E. C. Du Feu, F. J. McQuillin and R. Robinson *J. Chem. Soc.* 53 (1937).
[7] H. H. Zeiss and W. B. Martin, Jr., *J. Amer. Chem. Soc.* **75**, 5935 (1953).
[8a] A. Marchant and A. R. Pinder, *J. Chem. Soc.* 327 (1956); [b] S. M. McElvain and P. H. Parker, Jr., *J. Amer. Chem. Soc.* **78**, 5312 (1956).
[9] E. M. Kosower, *J. Amer. Chem. Soc.* **80**, 3253 (1958).

of the transition energies (i.e. the wavelength of the maximum transformed into kcal/mole by the relation $E_T = 2{\cdot}859 \times 10^{-3}\,\tilde{\nu}$ (in cm^{-1})) against **Z**, a new standard of solvent polarity.[9] The lines for the three ketones are shown in Fig. 1.

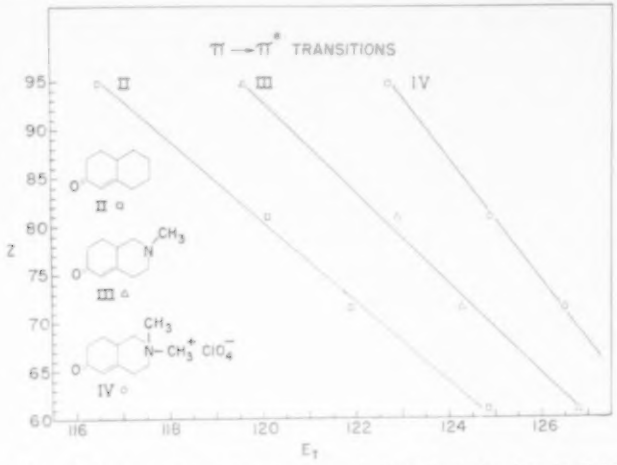

FIG. 1. A plot of the $\pi \rightarrow \pi^*$-transition energies derived from the data in Table 2 vs. the solvent polarity standard, **Z**.[9]

Grob *et al.*[10] have prepared a series of molecules in which the electrostatic effect of a positive charge upon an electronic transition can be observed. The structures involved were V and VI, 3-substituted-dehydroquinuclidines, and the principle utilized was to increase the electronegativity of the nitrogen by quaternization, and then to observe the longest wavelength band in a single solvent, 95% ethanol. Information concerning electron distribution in the excited state relative to the ground state was thus available by observing the direction and magnitude of the displacement

V VI

of the maximum, for the conversion V → VI. As expected, the positive charge on the nitrogen in VI destabilized excited states which produced positive charge at the adjacent carbon atom, and favored those which led to the accumulation of charge.

The $\pi \rightarrow \pi^*$-transition of an α,β-unsaturated ketone leads to an excited state with a greater contribution from the dipolar resonance form, $\overset{+}{C}—C=C—O^-$ than present in the ground state. The positive charge on nitrogen at position 3 in IV would (a) decrease the contribution of the dipolar resonance form to the ground state and (b) oppose to an even greater extent the formation of an excited state with increased charge separation. Introduction of the positive charge should lead to a displacement of the maximum to shorter wavelengths. In addition, the smaller dipoles of the ground and excited states would lead to a decreased sensitivity to solvent. *Both effects* can be seen in Fig. 1.

[10] C. A. Grob, A. Kaiser and E. Renk, *Chem. & Ind.* 598 (1957).

In order to examine the displacement of the maximum in a more quantitative fashion, certain facts are required about the ground states of the ketones which can be derived from measurements of the solvent sensitivities of the long wavelength $n \rightarrow \pi^*$-transitions. The long wavelength, low intensity maxima for ketones (II) and (IV) are listed in Table 3. Unfortunately, the maxima for the aminoketone (III) in most solvents were "buried" in the much more intense $\pi \rightarrow \pi^*$-transition, precluding a precise treatment of the maxima for this molecule.

TABLE 3. $n \rightarrow \pi^*$-TRANSITIONS

COMPOUND	II		IV	
Solvent	λ_{max} (Å)	ε_{max}	λ_{max} (Å)	ε_{max}
Water	—		3080	(52)
95% Ethanol	3085	(66)	3185	(37)
Acetonitrile	3240	(46)	3305	(31)
*cyclo*Hexane[a]	3370	(37)	—	—

[a] In *iso*octane, the $n \rightarrow \pi^*$-transition for the aminoketone, (III), had a λ_{max} 3370 (ε 41). It is interesting to note from Fig. 2 that the quaternary salt might be expected to have a $n \rightarrow \pi^*$-transition at 3390 Å.

The transition energies derived from the maxima reported in Table 3 are plotted against Z in Fig. 2, and are reasonably linear in this parameter. A number of other $n \rightarrow \pi^*$-transitions have previously been found to be linear in Z, including that of the α,β-unsaturated ketone, mesityl oxide.[4] The long wavelength transition for the

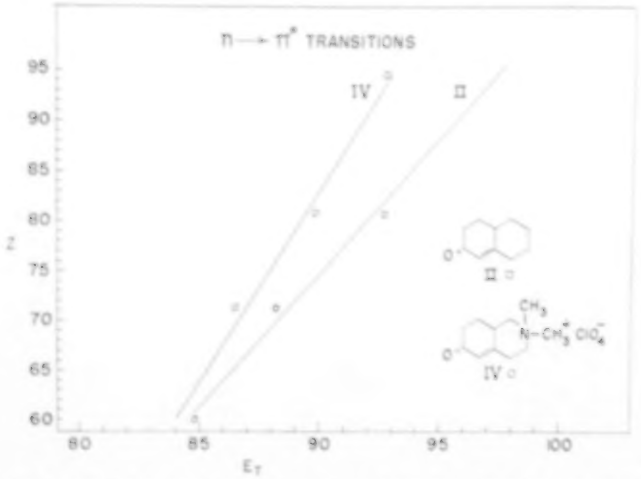

FIG. 2. A plot of the $n \rightarrow \pi^*$-transition energies for the carbocyclic ketone, II, and the quaternary ion, IV, derived from the data in Table 3 vs. the solvent polarity standard, Z.

quaternary salt, (IV), is considerably less sensitive to the solvent than the corresponding transition of the carbocyclic ketone, (II). The dipole moment due to the $\alpha:\beta$-unsaturated ketone portion of the quaternary ion, (IV), must be smaller than that of (II) on the reasonable assumption that solvent sensitivity depends upon the magnitude of the dipole moment. It is further assumed that the interaction with the solvent is roughly linear in the dipole moment for these two similarly shaped molecules.[4] The dipole moment of (II) may be taken as 4·00 D,* and the dipole moment for the $\alpha:\beta$-unsaturated ketone system of (IV) estimated as 2·72 D. The latter value leads to an estimate of 2·5 kcal/mole for the interaction of the $\alpha:\beta$-unsaturated ketone system portion of the molecule with water as compared with *iso*octane (or *cyclo*hexane).[4]

A method for calculating the dipole moments of the excited states of solvent sensitive electronic transitions has recently been published.[4] The information required for the calculation is (a) the difference between the transition energies in water and *iso*octane, (b) the interaction of the ground state with water, taking *iso*octane as a reference level, and (c) the Z-value difference for the pair of solvents used, in this case, *iso*octane and water.† The $\pi \rightarrow \pi^*$-transition energy for the quaternary ion is *iso*octane was estimated from the straight line shown in Fig. 1. The dipole moments thus calculated along with those estimated for the ground states are given in Table 4.

TABLE 4. DIPOLE MOMENTS

II IV

Ground state	4·00 D[11]	2·72 D[a,11]
Excited state	9·6 D	6·4 D[11]

[a] See text. [11] Moment of $\alpha:\beta$ unsaturated ketone portion of molecule only.

The charge distributions for the model structure, (VII), can be calculated from the equation, $\mu = er$, using $r = 3{\cdot}55$ Å, and are presented for both ground and excited states in Table 5.

VII

Formula (VII) allows a clear view of the repulsion that would exist between the positive charge at position 6- and any positive charge at position 3-. Inasmuch as

* The dipole moment of 3:5-dimethyl-2-*cyclo*hexen-1-one has been reported as 4·00 D.[11]

† In principle, any solvent pair would be suitable for this type of calculation, but the danger of specific interactions is clearly less for a hydrocarbon solvent-hydroxylic solvent combination. It is presumed that only negligible differences would exist between such solvents as *iso*octane and *cyclo*hexane, and the names are used interchangably in the present connection.

[11] J. B. Bentley, K. B. Everard, R. J. B. Marsden and L. E. Sutton, *J. Chem. Soc.* 2957 (1949).

the positive charge is increased in the excited state of the quaternary ion (IV), the increased repulsion between 6- and 3- should make excitation more difficult, i.e. require more energy. The magnitude of the increase should be directly related to the electrostatic repulsion between the charge at 3- and the *increase* in charge at the positive end of the conjugated system.

TABLE 5. CHARGE DISTRIBUTIONS[11]

Ground state	0·24	0·16
Excited state	0·56	0·38

[11] As fractions of a unit charge at one position, i.e. 6- in (VII).

Before presenting the calculation, it is necessary to point out that the charge distributions are derived directly or indirectly from experimental data, and do not at any point represent a hidden comparison between the positions of the $\pi \rightarrow \pi^*$-transitions of the ketones (II) and (IV). The assumption is also made that there is an intrinsic $\pi \rightarrow \pi^*$-transition energy for an $\alpha{:}\beta$-unsaturated ketone system of the type found in (II). A similar, much less restrictive assumption was implied in the development of the Woodward rules,[1] where the substituents are introduced directly on the conjugated system.

The electrostatic repulsive energy can be calculated with the equation 1, taking $D = 2{\cdot}0$ and r_{6-3} as 3·1 Å.* The repulsive energy should represent

$$E = q_1 q_2 / Dr \qquad (1)$$

the extra energy required for the $\pi \rightarrow \pi^*$-transition of the quaternary ion (IV) over that needed for the carbocyclic ketone, (II). The repulsive energy amounts to $11{\cdot}8 \pm 0{\cdot}8$ kcal/mole and must be corrected for the attractive counteracting force between the positive charge at 3 and the O^- connected to position 8, and located at a distance of $6{\cdot}5 \pm 0{\cdot}1$ Å from the nitrogen. The attractive force is $5{\cdot}6 \pm 0{\cdot}2$ kcal/mole. The net "extra" energy required for the transition is thus calculated as $6{\cdot}2 \pm 1{\cdot}0$ kcal/mole. *It is found experimentally that the increase in transition energy for the quaternary ion in water over that for the carbocyclic ketone is* $6{\cdot}2 \pm 0{\cdot}6$ kcal/mole. The agreement between the calculated and experimental results permits the conclusion that electrostatic repulsion is responsible for most of the shift in absorption maximum when H is $N(CH_3)_2^+$ in formula I.

The spectroscopic characteristics of the aminoketone (III) did not permit an assessment of the charge distributions present in the ground and excited states. Hall[12] found that a series of electronegative replacements, **H**, in the 4-position of the piperidine ring, (VIII), reduce the basicity. From the value for **H** = NH, and including a correction for the fact that there are 2 NH groups, it may be estimated that the electrical effect of an NH group is equivalent to 0·04 of a positive charge. The use of such an equivalent positive charge does not lead to any reasonable value

[12] H. K. Hall, Jr. *J. Amer. Chem. Soc.* **78**, 2570 (1956).

for the difference in ground and excited state charge-distributions for the amino-ketone (III). However, is seems likely that the electronegativity of the nitrogen is

VIII

overcome to some extent by the opportunities for hydrogen-bonding by the protonated ion, and that the equivalent charge given is a minimum value.

CONCLUSIONS

The preceding discussion has illustrated the use of Z-values in calculating certain excited state dipole moments and in rationalizing in a satisfactory fashion the effect of a positive charge on the position of absorption of an $\alpha:\beta$-unsaturated ketone. Further studies on such systems, especially (I) with different H, offer interesting possibilities for evaluating long-range electrical effects in organic molecules. No single, simple measurement will provide accurate information;[9] it appears especially necessary to learn about the variation of both $\pi \rightarrow \pi^*$ and $n \rightarrow \pi^*$-transitions with solvent. The technique of solvent variation is also useful in establishing that the transitions under study are indeed related to recognizable types.†

EXPERIMENTAL

Spectra. All spectra were measured in Spectrograde or purified solvents with a Cary recording spectrophotometer, Model 11 at about 25°. The $n \rightarrow \pi^*$-transitions had more than one band in *cyclo*hexane; the most intense absorption band was used to obtain λ_{max} as listed in Table 3.

3-*Methyl*-3-*azabicyclo*[4.4.0]-*dec*-6-*ene*-8-*one* (III). This aminoketone was prepared by the method of McElvain and Parker,[8] and was freshly distilled prior to spectroscopic examination. The methiodide, prepared in ether, was crystallized from ethanol.

3:3-*Dimethyl*-3-*azabicyclo*[4.4.0]-*dec*-6-*ene*-8-*one ion perchlorate.* To a solution of 8·19 g (0·0266 mole) of the methiodide (III) in 25 ml water was added slowly a solution of 5·47 g (0·0264 mole) silver perchlorate in 10 ml water. The silver iodide formed was removed by filtration, and the clear aqueous solution was passed through 50 g amberlite IR 45 resin prepared as follows: 50 g of the resin were washed with two 250 ml portions water. After decanting the second wash, the resin was treated with 300 ml 4·5 M perchloric acid for 30 min. The column prepared from this resin was then washed with water until the eluate no longer tested acid to Congo red paper (36–40 l.).

The aqueous solution of quaternary perchlorate eluted from this column was evaporated to dryness at 40–45° under reduced pressure. The crystalline residue was readily recrystallized from either water or aqueous ethanol, m.p. 196–197°.

(Found: C, 47·44; H, 6·40; Calc. for $C_{11}H_{18}O_5NCl$: C, 47·23; H, 6·49%).

* The distance between positions 6 and 3 was estimated with Catalin Molecular Models as 3·1 ± 0·1 Å A calculation[12] indicated a slightly smaller figure, using the *cyclo*hexylidene structure as the model.

† The compound which has an acetyl group in place of the methyl group at the 3-position of the amino-ketone (III) does not give a linear plot of transition energies against Z. The explanation for its special behaviour will be reported elsewhere (unpublished results).

[12] E. J. Corey and R. A. Sneen, *J. Amer. Chem. Soc.* **77**, 2505 (1955).

Tetrahedron, 1959, Vol. 5, pp. 288 to 292. Pergamon Press Ltd. Printed in Northern Ireland

THE DIRECT INTRODUCTION OF THE DIAZONIUM GROUP INTO AROMATIC NUCLEI—VI

REACTION MECHANISMS

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(*Received* 14 *August* 1958)

Abstract—Mechanisms are put forward to explain the formation of diazonium salts by the direct interaction of nitrous acid derivatives with aromatic compounds under a variety of conditions.

SINCE the preliminary communication[1] considerable work has been done,[2-7] and we feel the investigation has now reached a stage where sufficient data is available to make speculation about possible reaction mechanisms worthwhile. The purpose of the present paper is to collect together all the relevant data, largely from work already described in previous papers in this series or from earlier work and to show that all the results so far obtained can be explained in terms of very simple reaction mechanisms. Three rather different procedures have been used to introduce the diazonium group into aromatic compounds. Phenols and tertiary amines have been treated with nitrous acid in dilute aqueous or alcoholic media;[2,4,6,7] phenol ethers and poly-alkylbenzenes have been treated with nitrous acid in strongly acidic media such as concentrated sulphuric acid;[2,5,8] finally deactivated compounds such as nitro-derivatives have been treated with nitrous acid and catalytic amounts of mercuric ions in concentrated sulphuric acid.[3] Evidence has already been given to show that in the last case mercuration is the initial reaction. The first point to establish is that all these reactions proceed via nitroso-compounds.

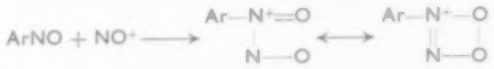
(i) *Evidence that nitroso-compounds are invariably intermediates*

It has previously been shown that, with each of the above methods for introducing the diazonium group, nitroso-compounds occur among the reaction products and that the nitroso-compound so formed when returned to a similar reaction system is converted into a diazonium salt. This does not establish that all the diazonium salt is formed in this way, for the route via the nitroso-compound might only be of minor importance and some as yet unknown direct route be the chief mechanism. We now have evidence for all three methods that *all* the diazonium salt is formed via the nitroso-compound. *p*-Cresol is converted into the corresponding diazonium salt by buffered nitrous acid in 77% yield.[6] If cupric ions are added to this solution the

[1] J. M. Tedder, *Tetrahedron* **1**, 270 (1957).
[2] J. M. Tedder, *J. Chem. Soc.* 4003 (1957).
[3] J. M. Tedder and G. Theaker, *J. Chem. Soc.* 4008 (1957).
[4] J. M. Tedder and G. Theaker, *Chem. & Ind.* 1485 (1957).
[5] J. M. Tedder, *J. Amer. Chem. Soc.* **79**, 6090 (1957).
[6] J. M. Tedder and G. Theaker, *J. Chem. Soc.* 2573 (1958).
[7] J. M. Tedder and G. Theaker, *J. Chem. Soc.* In press.
[8] E. J. Bourne, M. Stacey, J. C. Tatlow and J. M. Tedder, *J. Chem. Soc.* 1695 (1952).

formation of the diazonium salt is almost completely suppressed. The cupric ions trap the nitroso-compound as a chelate and prevent it from being converted into the diazonium salt, as it rapidly is by such solutions in the absence of copper. These facts clearly establish the nitroso-compound as an essential intermediate in this case.

The reactions carried out in strongly acid media are more complicated. At first we assumed that the diazonium salt was actually formed in the strong acid solution, but it has now been found that no diazonium salt is formed until the reaction mixture is poured into water. All the reactions in strong acid media are accompanied by very intense red-brown colours. We believe that these colours are due to a complex ion formed between the nitroso-compound and the nitrosonium ion.



Such colours can be produced by adding nitrosobenzene to concentrated solutions of sodium nitrite in sulphuric acid. Similar complexes have been proposed for nitrosoamines.[9] These complexes may be important in protecting the nitroso-group from further reaction in the concentrated sulphuric acid.[10] The reaction procedures used to prepare diazonium salts from mesitylene[2] (a typical strong acid preparation) and from *p*-nitroanisole[3] (a mercury catalysed reaction) have been repeated exactly as before, only instead of pouring the reaction mixtures into crushed ice, they were poured into cold sulphamic acid solution. In both cases only traces of diazonium salt were detected. In the latter example an 88% yield of crude 2-nitroso-4-nitroanisole was isolated (cf. a 75% yield of diazonium salt when poured into water).[3] In the former case the yield of diazonium salt was reduced to less than 15% (cf. a 78% yield when poured into water[2]) but the nitrosomesitylene could not be isolated from the nitrobenzene used as solvent. Not only do these results show that the nitroso-compound is an essential intermediate in the preparation of diazonium salts by either of these procedures, but clearly the mercuration procedure[3] could be adapted for the preparation of nitroso-compounds. It also seemed likely that the yields of diazonium salt could be improved by pouring the acid solutions into nitrous acid instead of water. This has been confirmed with *p*-nitroanisole when the yield was raised from 72·5% when poured into water, to 79·0% when poured into nitrous acid.

(ii) *The mechanisms of the nitrosations*

It is not the purpose of the present paper to draw any definite conclusions as to the exact mechanisms of the nitrosation steps. However certain inferences can be drawn from the data already available. Phenols and tertiary amines are nitrosated in very weakly acidic media, if diazonium salts are desired as the end products, and under these conditions only a limited number of nitrosating species are available. The most likely are HNO_2, N_2O_3 and NOCl. Less likely is $H_2NO_2^+$ and NO^+ can be discounted in such weakly acidic systems. On the basis of the work of Ingold, Hughes and their collaborators[11] N_2O_3 is the strongest candidate as the effective species, since in *qualitative* experiments chloride ion appears to have very little

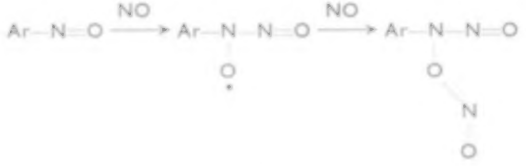
[9] C. C. Addison, N. Hodge and J. C. Sheddon, *Chem. & Ind.* 1338 (1953).
[10] E. Bamberger, H. Büsdorf and H. Sand, *Ber. Dtsch. Chem. Ges.* **31**, 1513 (1898).
[11] E. D. Hughes, C. K. Ingold and J. H. Ridd, *J. Chem. Soc.* 88 (1958).

accelerating effect. On the other hand nitrosation by ethyl nitrite and hydrogen chloride in anhydrous ethanol[4,6] probably involves molecular NOCl.

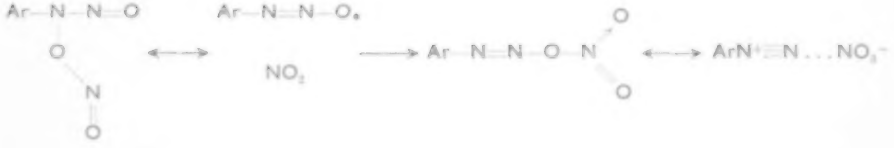
The reactions in more strongly acidic media[2,3,5,8] almost certainly involve nitrosation by the nitrosonium ion[12] and all the results so far obtained are consistent with such an hypothesis. In the mercury catalysed reaction the nitrosonium ion is probably also the species which displaces the mercuric ion, since this replacement will only occur in strongly acidic media.

(iii) *The conversion of the nitroso-compound into the diazonium salt*

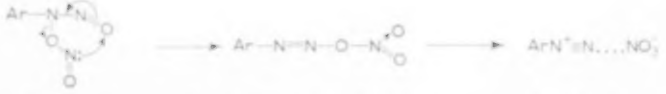
Whereas there are three very different conditions for the nitrosation, the conversion of the nitroso-compound into the diazonium salt always occurs in dilute nitrous acid in all the procedures developed so far. Bamberger showed that nitric oxide will convert nitrosobenzene into benzene diazonium nitrate and later that sodium nitrite in acetic acid will do the same.[13] He was unable to establish the stoicheiometry of the reaction definitely, but recently Havinga and his co-workers have shown that three moles of nitrite are necessary in the acetic acid system.[14] We have found that nitrosobenzene in nitrobenzene solutions absorbs almost exactly two moles of nitric oxide; unfortunately the yield of azo-dye obtained by coupling the resulting diazonium salt was not quantitative (75%) so that the stoicheiometry of this reaction is still not completely established. However, if just two moles of nitric oxide are assumed to be involved as suggested by the above result, a simple addition mechanism seems probable.



To be followed by either a dissociation and readdition;

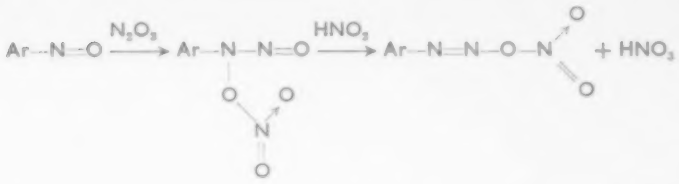


or an intramolecular rearrangement.



In solution the reactive entity is likely to be dinitrogen trioxide instead of nitric oxide and this would readily explain the difference in the observed stoicheiometry.

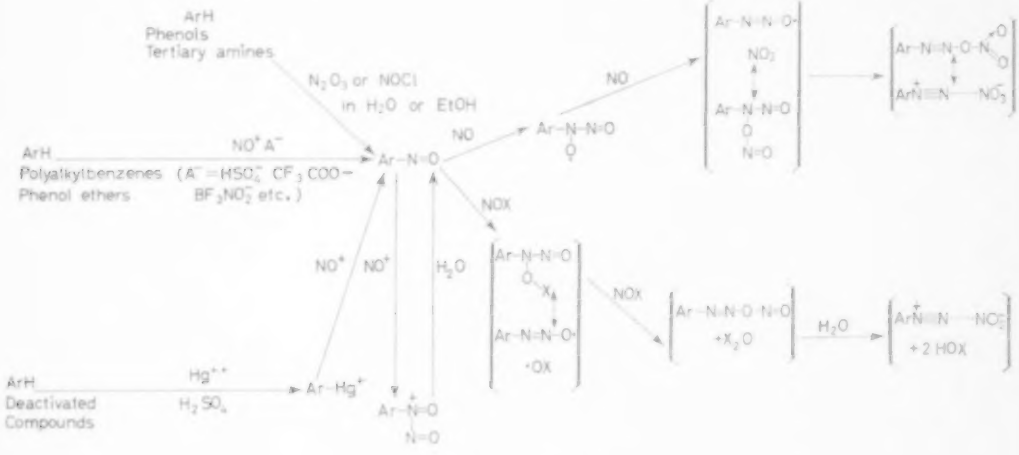
[12] C. A. Bunton, E. D. Hughes, C. K. Ingold, D. I. H. Jacobs, M. H. Jones, G. J. Minkoff and R. I. Reed, *J. Chem. Soc.* 2628 (1950).
[13] E. Bamberger, *Ber. Dtsch. Chem. Ges.* **30**, 506 (1877); *Ibid.* **51**, 634 (1918).
[14] A. Kraaijeveld and E. Havinga, *Rec. Trav. Chim.* **73**, 549 (1954).



Clearly similar mechanisms can be visualised for a variety of nitrosyl derivatives NOX.

(iv) *Conclusions*

We believe we have established unequivocally the two stage nature of the reaction involving a nitroso-intermediate. There appear to be several mechanisms leading to the formation of the nitroso-compounds and similarly a number of closely related mechanisms for the conversion of the nitroso-compound into the diazonium salt. It has not been possible so far to attempt thorough investigations to elucidate the exact details of these steps; however, our present qualitative ideas about these mechanisms have proved of the utmost value when attempting to extend the reaction and for this reason we are presenting them now. They are summarised in the following scheme.



EXPERIMENTAL

Experiments to halt the reaction at the nitroso-stage

(a) p-*Cresol nitrosated in the presence of cupric ions.* *p*-Cresol (1·08 g) was dissolved in acetone (50 cc) and the solution diluted with water (100 cc). Sodium nitrite (10 g) were dissolved and cupric acetate (10 g) were added. Not all the cupric acetate dissolved. The mixture was cooled to 0° and 2 N HCl (20 cc) were added. After 20 hr a 50 cc portion was withdrawn and the excess nitrous acid removed by the addition of sulphamic acid solution. The solution, which was an intense purple colour, was extracted with light petroleum (b.p. 60–80°) and the aqueous layer treated with a slight excess of 2 N NaOH solution. The copper hydroxide was removed by filtration and the clear yellow liquid rendered just acid. Excess resorcinol was added and the solution was made alkaline and left

for an hour before reacidification. A trace of dye (0·01 g) was precipitated (cf. 0·51 g in the absence of copper ions).

(b) *Mesitylene treated with sodium nitrite and sulphuric acid in nitrobenzene and then poured into sulphamic acid solution.* Sodium nitrite (4·2 g) was dissolved in concentrated sulphuric acid (10 cc). Nitrobenzene (10 cc) was added to the cooled paste. Mesitylene (1 cc) was added at 20° and the mixture frequently stirred by hand during a 4 hr reaction.[3] The mixture was then treated with sulphamic acid (7 g) poured into a solution of sulphamic acid (7 g) in ice/water (200 g) and ether extracted (green solution). The aqueous portion was coupled with excess β-naphthol. Yield of crude mesitylene-azo-β-naphthol, red solid, m.p. 127–131°, was 0·32 g (15% theory). Attempts to isolate the nitrosomesitylene from the ethereal/nitrobenzene solution were not successful. However, presence of nitroso-compound was established qualitatively (Liebermann test).

(c) *Preparation of 2-nitroso-4-nitroanisole.* *p*-Nitroanisole (3·06 g) was dissolved in concentrated sulphuric acid (15 cc) containing mercuric oxide (0·043 g) at 20°. A solution of sodium nitrite (6·90 g) in concentrated sulphuric acid (30 cc) was added evenly during 3 hr at 20°.[3] After 3 hr further reaction at 20° the mixture was treated with sulphamic acid (10 g) and the whole poured carefully into ice/water (500 g) containing sulphamic acid (10 g). The buff coloured precipitate was filtered off (3·20 g 88%, m.p. 109–112°). (The filtrate was tested for the presence of diazonium salt—only a trace was detected). The crude nitroso-compound was recrystallised three times from aqueous acetic acid (plus charcoal) as pale yellow plates, m.p. alone, or in admixture with pure 2-nitroso-4-nitroanisole,[3] 123–124°. The u.v. spectrum was compared with that of the authentic material and found identical; the spectrum of the crude material indicated that it was 90·0% 2-nitroso-4-nitroanisole.

Improving the yield of 2-diazo-4-nitroanisole by pouring the reaction products into nitrous acid

p-Nitroanisole was treated with mercuric oxide and sodium nitrite in concentrated sulphuric acid as above, (c). After 3 hr reaction at 20°, aliquots (ca. 2·0 g) were removed and treated as follows:—

(a) reaction mixture poured into ice/water (100 g), treated immediately with a slight excess of sulphamic acid solution, neutralised with sodium acetate and coupled with an excess of a standard solution of 3-methyl-1-*p*-sulphophenyl-5-pyrazolone solution containing sodium acetate.[3] After a suitable period for completion of coupling, the excess of pyrazolone was back-titrated with standard *p*-nitrobenzene diazonium-chloride solution using the sodium salt of H-acid solution as external indicator. Yield of diazonium salt as above was 72·5%.

(b) mixture poured into ice/water containing sodium nitrite (2 g) and reaction allowed to proceed for 30 min. A slight excess of sulphamic acid was then added and the yield estimated as above. Yield of diazonium salt was 79·0%.

Reaction of nitric oxide with nitrosobenzene

Purified nitrosobenzene (approx 0·2 g) was added to nitrobenzene (20 ml) saturated with nitric oxide and contained in a 50 ml conical reaction vessel attached to a simple low pressure "hydrogenation" apparatus containing pure nitric oxide in the storage burette. The reaction was carried out with stirring at 20° for up to 25 hr, until no more gas was absorbed, the reaction vessel being covered with dark paper. From two experiments, the absorption of nitric oxide by nitrosobenzene was 2·21 and 1·88 moles per mole. The reaction mixture was then poured into water (100 cc) and the nitrobenzene separated and the aqueous solution coupled with excess β-naphthol. The yield of crude benzene-azo-β-naphthol, m.p. 122–4°, was 0·383 g (from nitrosobenzene (0·22 g) and 2·21 moles/mole nitric oxide) equivalent to a 75% yield.

Acknowledgements—The authors wish to acknowledge many valuable discussions with their colleagues both in Sheffield and elsewhere, which greatly contributed to the development of the mechanism described here.

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ANODIC REDUCTIONS—V*

THE REDUCTION OF DIKETONES BY UNIPOSITIVE MAGNESIUM ANODICALLY GENERATED

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(*Received* 18 *August* 1958)

Abstract—A series of diketones of the general formula $C_6H_5CO(CH_2)nCOC_6H_5$ has been prepared and subjected to "anodic reduction" in sodium iodide-pyridine solution between magnesium electrodes. In every case hydrolysis of the anolyte following electrolysis yielded a 1:2-diol as the reduction product as evidenced by titration with standard lead tetraacetate solution. The diketones, 1:3-dibenzoylpropane ($n = 3$) and 1:4-dibenzoylbutane ($n = 4$), gave *cis*-1:2-diphenyl*cyclo*pentane-1:2-diol and *cis*-1:2-diphenyl*cyclo*hexane-1:2-diol, respectively. On the assumption that the other diketones also gave cyclic 1:2-diols, there is a striking correlation between the initial mean valence number (V_i) of the magnesium entering solution from the anode and the size of the ring; the lowest V_i values were obtained in those instances where the diketones originally in solution gave the most stable cyclic diols. Interpretations are offered for these results and for corrosion phenomena observed.

A SUBSTANTIAL amount of evidence has been accumulated which indicates that on anodic oxidation in aqueous salt solutions magnesium enters solution at least in part in the unipositive state.[1–3] The latter species has not been isolated in the form of a compound, but is converted rapidly to the dipositive cation as a result of oxidation by the solvent, reducible solutes (e.g. $AgNO_3$, $KMnO_4$), or electrochemically at the anode.

The anodic behavior of magnesium in anhydrous pyridine solutions has also been investigated. This solvent has the advantage over water in that it is reduced only with great difficulty, but is nevertheless a satisfactory electrolytic medium. It has therefore proved to be a useful solvent for study of the effects of organic oxidants on the anodic behavior of magnesium.

In the anodic oxidation of magnesium in sodium iodide-pyridine medium the metal entered solution with an initial mean valence number (V_i) of two.[4] However, in the presence of any one of a number of potential organic oxidants (e.g. benzophenone,[4] 4:4′-dimethylbenzophenone,[5] 2′-methoxy-2:4:6-trimethylbenzophenone,[6] benzil,[5] nitrobenzene,[7] nitrosobenzene,[7] azoxybenzene,[7] and azobenzene[7]) the magnesium went into solution with an initial mean valence number significantly less than two. Under these circumstances a reduction product of the organic additive was isolated from the anolyte, and in a majority of instances the amount of reduction product corresponded essentially quantitatively to that expected from oxidation by the organic additive of the metal from its initial mean valence state to its common

* For Part IV see ref. 7.

[1] M. D. Rausch, W. E. McEwen and J. Kleinberg, *Chem. Rev.* **57**, 417 (1957).
[2] J. H. Greenblatt, *J. Electrochem. Soc.* **103**, 539 (1956).
[3] D. V. Kokouliva and B. N. Kabanov, *Dokl. Akad. Nauk SSSR* **112**, 692 (1957).
[4] M. D. Rausch, W. E. McEwen and J. Kleinberg, *J. Amer. Chem. Soc.* **76**, 3622 (1954).
[5] W. E. McEwen, J. Kleinberg, D. L. Burdick, W. D. Hoffman and J. Y. Yang, *J. Amer. Chem. Soc.* **78**, 4587 (1956).
[6] M. D. Rausch, F. D. Popp, W. E. McEwen and J. Kleinberg, *J. Org. Chem.* **21**, 212 (1956).
[7] J. Y. Yang, W. E. McEwen and J. Kleinberg, *J. Amer. Chem. Soc.* **80**, 4300 (1958).

+2 state. It should be emphasized that in only a few of the cases studied was the organic additive itself capable of attacking the massive magnesium anode non-electrolytically. The "anodic reductions" effected in pyridine solution, like those in aqueous solution, are interpreted as being brought about by the action of unipositive magnesium anodically generated.

Although pyridine solutions of the organic additives investigated generally were unreactive toward massive magnesium, primary products of "anodic reduction" were found to be sufficiently reactive to attack the metal. Considerable evidence has been obtained that these primary reduction products are radical-ions and that corrosion proceeds by a chain mechanism in which the radical-ions and unipositive magnesium function as chain carriers.[1,8]

A series of diketones of the general formula $C_6H_5CO(CH_2)_nCOC_6H_5$, where n equals two through eight, has now been prepared and subjected to "anodic reduction". The only diketone previously studied was benzil;[3] this was quantitatively reduced to a product which on hydrolysis gave benzoin. On the other hand, simple aromatic ketones, such as benzophenone[4] and 4:4′-dimethylbenzophenone,[5] afforded pinacols on hydrolysis of the anolyte following electrolysis. It was felt, therefore, that "anodic reduction" of diketones having the carbonyl groups separated by varying numbers of methylene groups would give cyclic 1:2-diols (i.e. cyclic pinacols). Furthermore, on the basis of a previously proposed mechanism for the anodic oxidation of magnesium,[1] it was anticipated that there would be a correlation between the initial mean valence number with which the metal entered solution and the size of the carbocylic ring of the diol formed. As a matter of fact, both expectations were realized.

With every diketone, "anodic reduction" and subsequent hydrolysis of the anolyte yielded a 1:2-diol as evidenced by titration with standard lead tetra-acetate solution. The most intensive studies were carried out with 1:3-dibenzoylpropane ($n = 3$) as the organic additive. Hydrolysis of the anolyte yielded a cyclic diol to which Criegee *et al.*[9] have assigned the structure *cis*-1:2-diphenyl*cyclo*pentane-1:2-diol (I) on the basis of its very rapid rate of cleavage with lead tetraacetate solution and its color reaction with potassium "triacetylosmate." However, owing to the fact that only one of the geometrical isomers has ever been prepared, it seemed desirable to provide more substantial evidence for the configuration. That the compound actually possessed the *cis* structure was proved by the demonstration of the existence of intramolecular hydrogen bonding according to the infrared spectral method of Kuhn,[10,11] by the formation of the *iso*propylidene derivative of the *cyclo*pentanediol,[12,13] and the conversion of the diol to the appropriate cyclic ester with phenylboronic acid.[14] Although acid-catalyzed hydrolysis of the *iso*propylidene derivative gave only 2:2-diphenyl*cyclo*pentanone as a result of a pinacol-pinacolone rearrangement, alkaline hydrolysis of the phenylboronate ester afforded the original *cis* diol.

With 1:4-dibenzoylbutane ($n = 4$) as organic additive the situation was more complex than with 1:3-dibenzoylpropane. In addition to the formation of a cyclic

[8] D. L. Burdick, A. V. Santoro, W. E. McEwen and J. Kleinberg, *J. Amer. Chem. Soc.* **79**, 5467 (1957).
[9] R. Criegee E. Hoger, G. Huber, P. Kruck, F. Marktscheffel and H. Schellenberger, *Liebigs Ann.* **599**, 81 (1956).
[10] L. P. Kuhn, *J. Amer. Chem. Soc.* **74**, 2492 (1952).
[11] L. P. Kuhn, *J. Amer. Chem. Soc.* **76**, 4323 (1954).
[12] H. G. Derx, *Rec. Trav. Chim.* **41**, 318 (1922).
[13] J. Böeseken, *Bull. Soc. Chim. Fr.* (4) **53**, 1332 (1933).
[14] J. M. Sugihara and C. M. Bowman, *J Amer. Chem. Soc.* **80**, 2443 (1958).

1:2-diol, there was obtained 1-benzoyl-2-phenyl-1-*cyclo*pentene(II), a product formed by intramolecular condensation and dehydration of the starting ketone. The reduction product, 1:2-diphenyl*cyclo*hexane-1:2-diol, had the *cis* configuration as

I

shown by formation of the appropriate cyclic ester with phenylboronic acid and the appearance of absorption bands in the infrared spectrum denoting intramolecular hydrogen bonding.

II

Although the 1:2-diols were not actually isolated when the other diketones of the series were used as additives, there was obtained infrared evidence that the "anodic reduction" product of 1:8-dibenzoyloctane ($n = 8$) was a 1:2-diphenyl*cyclo*decane-1:2-diol. It seems reasonable to assume, on the basis of the evidence cited above for the *cyclo*pentane and *cyclo*hexane diols, that all of the diketones investigated gave cyclic *cis* diols.

It is significant that there was found a striking correlation between the initial mean valence number (V_i) of the magnesium entering solution from the anode and the stability of the ring of the 1:2-diol formed by "anodic reduction." The lowest V_i values were obtained in those instances where the diketones originally in solution gave the most stable cyclic diols, i.e. those containing five- and six-membered rings. Moreover, as the data of Fig. 1 show, there is a remarkable similarity between the

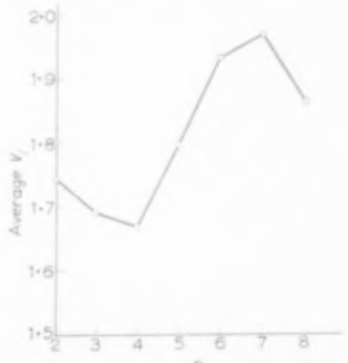


FIG. 1. Anodic behavior of magnesium metal in the presence of various diketones having the general formula $C_6H_5CO(CH_2)nCOC_6H_5$

curve obtained when V_i is plotted against ring size ($n + 2$) and those found when rate or equilibrium data of other reactions involving either the use or formation of ring compounds are plotted as functions of ring size.[11,15–18]

[15] V. Prelog, *J. Chem. Soc.* 420 (1950).
[16] H. C. Brown, R. S. Fletcher and R. B. Johannesen, *J. Amer. Chem. Soc.* **73**, 212 (1951).
[17] H. C. Brown and M. Borkawski, *J. Amer. Chem. Soc.* **74**, 1894 (1952).
[18] R. Heck and V. Prelog, *Helv. Chim. Acta* **38**, 1541 (1955).

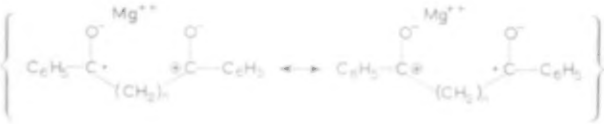
It is also of significance that the anolyte solutions following electrolyses in which the organic oxidant was 1:3-dibenzoylpropane were capable of corroding the massive magnesium employed as anode, whereas solutions of the diketone itself could not do so. The product of corrosion was *cis*-1:2-diphenyl*cyclo*pentane-1:2-diol(I), the same as obtained from electrolysis alone. Evidence of the same general nature as that provided previously in a study of the "anodic reduction" of benzophenone[8] was obtained which showed that the corrosion process proceeded by a free radical chain reaction. (See Experimental for details.)

The following mechanism is proposed to account for both the electrolytic and corrosion results cited above:

(1) The magnesium anode enters solution at least in part in the +1 state.[1]

(2) Part of the unipositive magnesium is oxidized to the common +2 state by diketone and part electrochemically at the surface of the anode. The relative rates of these competing reactions determine the initial mean valence number (V_i) observed in each experiment.

(3) To explain the variation of V_i with ring size of the product of "anodic reduction," it seems reasonable to assume that the diketone and the +1 magnesium react to give intermediate III.

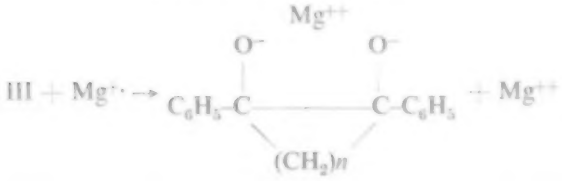


III

The stability and ease of formation of (III) is greatest when $n = 3$ or 4, and therefore, as a result of the competitive oxidation of unipositive magnesium given in (2), the V_i values are the lowest when the diketones are 1:3-dibenzoylpropane and 1:4-dibenzoylbutane.

(4) Before the magnesium salt (IV) of the ultimate cyclic diol can be formed, intermediate (III) must gain an additional electron. In the "anodic reduction" process, this extra electron can be provided by unipositive magnesium, whereas in the corrosion process the electron is obtained from massive magnesium:

"anodic reduction" process



IV

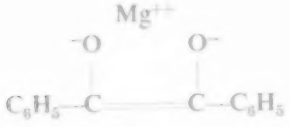
corrosion process (chain mechanism)

(a) $III + Mg \rightarrow IV + Mg^{+\cdot}$ (massive)

(b) $C_6H_5CO(CH_2)nCOC_6H_5 + Mg^{+\cdot} \rightarrow III + Mg^{++}$

It is likely that any of the intermediate (III) which is still present at the time of hydrolysis undergoes disproportionation to give the cyclic diol plus the original diketone.

As reported previously,[5] benzil on "anodic reduction" gives benzoin in quantitative yield. It is probable that the magnesium enolate(V) is the final reduction product existing in the anolyte prior to hydrolysis; it is clear that (V) may be regarded as the same general type of compound as (IV), but one in which $n = 0$. Furthermore, evidence has now been obtained that the radical-ion(VI) is formed by the initial reaction of unipositive magnesium with benzil. The species (VI) functions as a chain carrier in corrosion of massive magnesium following electrolysis.* The organic corrosion product, following hydrolysis of the reaction mixture, is also benzoin. Thus in "anodic reduction" and in subsequent corrosion behavior benzil acts in a manner strictly analogous to that of 1:3-dibenzoylpropane and presumably the other diketones investigated.



V

VI

Whereas the mechanism of "anodic reduction" presented above and in our previous papers is completely consistent with all the data thus far accumulated, it has been pointed out to us by the referee of a previous paper that there is a possible alternative mechanism, namely one involving simultaneous anodic-cathodic behavior of the magnesium rod which is normally regarded as the anode. On the basis of evidence published to date there is no way of distinguishing between these alternatives. However, although this matter is still open, it seems to us that the corrosion mechanism which involves unipositive magnesium as a chain carrier is firmly established.[8]

EXPERIMENTAL†

Materials. The 0·5 cm (diameter) magnesium rods which were used as the electrodes were cut from an 0·8 cm rod of 99·8% purity furnished by the Aluminum Company of America. The sodium iodide, "Baker's Analyzed," which was employed as the electrolyte was dried at a temp of 110° for several days before use. Pyridine, Mallinckrodt Analytical Reagent grade was fractionally distilled at atmospheric pressure from sodium through a 45 cm packed column and stored over anhydrous barium oxide. By an adaptation of a procedure described in *Organic Syntheses*[19] each of the following diketones was prepared: 1:3-dibenzoylethane, 1:4-dibenzoylpropane, 1:5-dibenzoylpentane, 1:6-dibenzoylhexane, 1:7-dibenzoylheptane, and 1:8 dibenzoyloctane. The melting points of the diketones agreed with the values

* For previous evidence regarding the existence of radical-ion (VI) see B. Venkataraman and G. K. Fraenkel, *J. Amer. Chem. Soc.* **77**, 2707 (1955) and J. L. Ihrig and R. G. Caldwell, *J. Amer. Chem. Soc.* **78**, 2097 (1955).

† All melting points are corrected. Analyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

[19] R. C. Fuson and J. T. Walker, *Organic Syntheses* (2nd Ed.) Coll. Vol. II, p.169. Wiley, New York (1943).

reported in the literature.[19–21] 1:2-Dibenzoylbutane was prepared by the reduction of 1:4-diphenyl-1:4-butenedione with stannous chloride.[21]

Apparatus and procedure. The divided cell used in the electrolyses was of the same type described by Davidson and Jirik.[22] The source of direct current was a full-wave mercury tube rectifier capable of supplying up to 1000 volts. A silver coulometer in series with the cell was employed to determine the quantity of current passed. The cell and its contents were immersed in a water bath which was maintained at $40 \pm 0{\cdot}1°$.

Before an electrolysis the magnesium electrodes (0·5 cm × 5 cm) were throughly cleaned with dilute nitric acid, washed with distilled water, and then dried and weighed. The sodium iodide solution (0·5 m in pyridine) was prepared in such a manner as to minimize exposure to air and moisture. For most experiments, 0·025 mole of diketone was dissolved in 100 ml of the sodium iodide-pyridine solution and then half of the resulting solution was added to each compartment of the electrolytic cell. The cell was swept with dry oxygen-free nitrogen both before and during each electrolysis. The duration of electrolysis, the applied voltage, and the current density will be specified below for the various types of experiments. On completion of electrolysis, the anode was washed successively with distilled water, acetone and distilled water. After the electrode had been dried and weighed, the initial mean valence number (V_i) was calculated in accordance with the equation

$$V_i = \frac{\text{wt of Ag deposited in coulometer} \times 24{\cdot}32}{107{\cdot}88 \times \text{wt of Mg lost from anode}}$$

Effect of nature of diketone on initial mean valence number. Four to six electrolyses were carried out with each diketone. Each electrolysis was conducted for a period of 2 hr at an applied voltage of 25–45 volts and an anodic current density of 0·003–0·006 amp/cm². The average initial mean valence numbers obtained with the various diketones were as follows: 1:2-dibenzoylethane, $1{\cdot}74 \pm 0{\cdot}02$; 1:3-dibenzoylpropane, $1{\cdot}69 \pm 0{\cdot}01$; 1:4-dibenzoylbutane, $1{\cdot}67 \pm 0{\cdot}02$; 1:5-dibenzoylpentane, $1{\cdot}80 \pm 0{\cdot}04$; 1:6-dibenzoylhexane, $1{\cdot}93 \pm 0{\cdot}05$; 1:7-dibenzoylheptane, $1{\cdot}97 \pm 0{\cdot}03$; 1:8-dibenzoyloctane, $1{\cdot}87 \pm 0{\cdot}01$.

"Anodic reduction" of 1:3-dibenzoylpropane. Electrolyses in which 1:3-dibenzoylpropane (0·025 m) was the organic additive gave initial mean valence numbers (V_i) for magnesium of 1·63 and 1·53. The time of electrolysis in each case was 24 hr, the applied voltage 25–50 volts, and the initial current density 0·005–0·007 amp/cm². On completion of each electrolysis, the contents of anolyte and catholyte were drained into separate flasks each containing 125 ml of freshly boiled 18% HCl cooled to 0° with cracked ice. The resulting anolyte solution was placed in a refrigerator for 24 hr and the precipitate which had formed collected by filtration. The filtrate was extracted with ether in a continuous extractor, and the precipitate was combined with the material recovered from the ether extract. The combined solid material was dissolved in chloroform and diluted to a volume of 250 ml.

[20] L. A. Wiles and E. C. Baughan, *J. Chem. Soc.* 933 (1953).
[21] P. S. Bailey and R. E. Lutz, *J. Amer. Chem. Soc.* **70**, 2412 (1948).
[22] A. W. Davidson and F. Jirik, *J. Amer. Chem. Soc.* **72**, 1700 (1950).

Appropriate aliquots were withdrawn, evaporated to dryness, and the quantity of 1:2-diol determined by titration with lead tetraacetate according to the procedure of Gebhart and Adams.[23] The lead tetraacetate solution was standardized against *cis*-1:2-diphenyl-1:2-*cyclo*pentanediol, prepared as described below. The yields of 1:2-diol, as found by titration, were 94% for the electrolysis which gave a V_t of 1·63 and 92% for that in which the V_t equalled 1·53, the theoretical yield being determined by the use of the equation:

$$\text{wt of 1:2-diol} = \frac{(2 - V_t)\,(\text{wt of Mg lost from anode})}{24{\cdot}32} \times \text{equiv. wt of 1:2-diol}$$

The yields were calculated on the assumption that the 1:2-diol formed was *cis*-1:2-diphenyl-1:2-*cyclo*pentanediol. As is shown below this assumption was a valid one.

Isolation of cis-1:2-*diphenyl*-1:2-cyclo*pentanediol from anolyte hydrolysate.* In an experiment designed to facilitate the isolation of the 1:2-diol, 2·0 g of 1:3-dibenzoylpropane was added to the sodium iodide-pyridine solution contained in the anode compartment. No organic additive was dissolved in the catholyte. Electrolysis was carried out for 16 hr under the same conditions as in the previous experiment; a V_t value of 1·35 was found.

The anolyte solution was hydrolyzed as described above, the resulting solution placed in a refrigerator for 24 hr, and then the precipitate (A) present filtered off. The filtrate was subjected to continuous extraction with ether and the resulting ether solution then washed with small amounts of dilute aqueous solutions of sodium besulfite, hydrochloric acid, sodium bicarbonate, and finally distilled water. Removal of the ether by distillation left 0·40 g of a solid material, which was dissolved in chloroform. The infrared spectrum of this solution was taken and found to be essentially identical with that of a chloroform solution of authentic *cis*-1:2-diphenyl-1:2-*cyclo*pentanediol (see below). Moreover, addition of petroleum ether (b.p. 38°) to the chloroform solution yielded 0·25 g of a crystalline material, m.p. 102–103°, which did not depress the melting point of authentic *cis*-1:2-diphenyl-1:2-*cyclo*pentanediol.

The original precipitate (A) was dissolved in chloroform and an appropriate aliquot titrated with standard lead tetraacetate solution as described previously. The precipitate was found to contain 0·14 g of 1:2-diol. The infrared spectrum of the chloroform solution showed that precipitate (A) consisted of a mixture of starting diketone (1:3-dibenzoylpropane) and *cis*-1:2-diphenyl-1:2-*cyclo*pentanediol.

The total yield of *cis*-1:2-diphenyl-1:2-*cyclo*pentanediol amounted to 0·54 g (theoretical 0·62 g, as calculated by the equation given in previous section).

cis-1:2-*Diphenyl*-1:2-cyclo*pentanediol.* By a method adapted from one described by Japp and Michie,[24] 1:3-dibenzoylpropane was reduced to a 1:2-diol which was identical with that obtained by "anodic reduction" of the diketone. After 2·00 g (0·074 mole) of aluminum foil had been cut up into pieces 1 cm in length, it was treated with a dilute aqueous solution of mercuric chloride for 2 min. The amalgamated aluminum pieces were collected by filtration, washed with ethanol and ether, and added to 200 ml of aqueous ethanol containing 67% (by volume) of the

[23] H. J. Gebhart, Jr. and K. H. Adams, *J. Amer. Chem. Soc.* **76**, 3925 (1954).
[24] F. R. Japp and A. C. Michie, *J. Chem. Soc.* **79**, 1020 (1901).

alcohol. To this mixture was added 5·00 g (0·002 mole) of 1:3-dibenzoylpropane, and the mixture was heated with stirring for 3 hr at a temp. slightly below the boiling point of ethanol. An additional 0·5 g of the amalgamated aluminum was added to the mixture, which was then stirred overnight. The mixture was heated to boiling and filtered hot. After the filtrate had been concentrated to one-third of its original volume, 2·5 g of the 1:2-diol crystallized from solution. The purified material had a m.p. of 102–103°; reported, 101°.[9]

(Found: C, 80·06; H, 7·19; Calc. for $C_{17}H_{18}O_2$: C, 80·32; H, 7·08%).

The elemental analysis, the fact that the infrared spectrum of the compound taken in chloroform solution showed the presence of hydroxyl groups but the absence of carbonyl groups, the oxidation of the compound to the original diketone by means of chromic acid,[24] and the quantitative cleavage by lead tetraacetate prove conclusively that the compound is ether *cis*- or *trans*-1:2-diphenyl-1:2-*cyclo*pentanediol.

While experiments to determine the configuration of the diol were in progress in this Laboratory, Criegee *et al.*[9] claimed that the compound possessed the *cis* configuration on the basis of its rapid rate of reaction with lead tetraacetate and the fact that it gave a positive color reaction with potassium "triacetylosmate." Inasmuch as only one isomer is known, the evidence for the *cis* configuration would appear not to be entirely conclusive. Therefore, several additional lines of evidence pertaining to the configuration were uncovered.

Infrared evidence for intramolecular hydrogen-bonding. The infrared evidence that the cyclic 1:2-diol possessed the *cis* configuration was obtained by the procedure of Kuhn.[10] In 50 ml of reagent grade carbon tetrachloride that had been dried over phosphorus pentoxide was dissolved 0·2523 g (0·001 mole) of the diol, m.p. 102°–103. Aliquots of this solution were taken and diluted to give a series of solutions of concentrations 0·002, 0·004, 0·01, and 0·02 M. Infrared spectra were taken and all four of the solutions showed absorption peaks at 3600 and 3540 cm^{-1}. Furthermore, the relative intensities of the peaks were essentially constant, showing that the hydrogen bonding which gives rise to the absorption peak at 3540 cm^{-1} is intramolecular and that the cyclic diol has the *cis* configuration.

Preparation of cis-1:2-*diphenyl*-1:2-cyclo*pentanediol phenylboronate.* To 1·12 g (0·009 mole) of phenylboronic acid dissolved in 4 ml of methanol was added 0·90 g (0·0035 mole) of the 1:2-diol, m.p. 102–103°. After warming to effect reaction, the mixture was cooled, filtered, and the precipitate washed with 10 ml of hot water, 5 ml of cold methanol, and then dried in an oven at 110°. There was obtained 1·06 g (90%) of the ester, which on recrystallization from absolute methanol-benzene had an m.p. of 158·8–159·2°.

(Found: C, 81·31; H, 6·25; B, 3·41; Calc. for $C_{23}H_{21}BO_2$: C, 81·19; H, 6·22; B, 3·18%).

It has been established[14] that *cis*-1:2-*cyclo*pentanediol gives a phenylboronate ester of molecular formula $C_{11}H_{13}BO_2$, whereas the *trans* diol yields an ester of molecular formula $C_{17}H_{18}B_2O_2$. The isomeric 1:2-*cyclo*hexanediols behave analogously. Therefore, inasmuch as the 1:2-diphenyl-1:2-*cyclo*pentanediol of m.p. 102–103° gives a phenylboronate having but one phenylboronate moiety, it can be concluded that the cyclic diol has the *cis* configuration.

Hydrolysis of the phenylboronate. To a solution of 20 ml of dioxane in 100 ml

of water was added 6·0 g of sodium hydroxide and 0·5 g of *cis*-1:2-diphenyl-1:2-*cyclo*pentanediol phenylboronate. The resulting solution was refluxed for 1 hr and extracted with ether. After the ether extract had been washed with water and dried over anhydrous sodium sulfate, the ether was removed by distillation and the residue recrystallized from chloroform–petroleum ether solution. There was obtained a white crystalline compound, m.p. 102–103°, which did not depress the melting point of authentic *cis*-1:2-diphenyl-1:2-*cyclo*pentanediol.

Preparation of the iso*propylidine ketal of* cis-1:2-*diphenyl*-1:2-cyclo*pentane-diol.* To a solution of 5·00 g (0·02 mole) of the 1:2-diol, m.p. 102–103°, in 100 ml of highly purified acetone contained in an Erlenmeyer flask, was added 1 ml of conc sulfuric acid. The flask was stoppered tightly and allowed to stand for 12 hr at room temp. Most of the solvent was then removed by distillation under reduced pressure and an aqueous solution containing 5 g of potassium carbonate added. The organic material was extracted into ether, the ether solution dried over anhydrous sodium sulfate and the solvent removed by distillation. The residue was dissolved in petroleum ether, b.p. 38°, and chromographed on alumina. Elution with petroleum ether provided 0·8 g of white solid which had an m.p. of 84–85° after recrystallization from *n*–hexane.

(Found: C, 81·53; H, 7·29; Calc. for $C_{20}H_{22}O_2$: C, 81·58; H, 7·53%).

Hydrolysis and rearrangement of the iso*propylidine ketal.* A solution of 0·2 g of the *iso*propylidine ketal, m.p. 84–85°, in 3·0 ml of 87% formic acid was heated on a steam bath for 50 min. The solution was made alkaline with sodium hydroxide solution and extracted with chloroform. The chloroform solution was dried over anhydrous magnesium sulfate and evaporated, giving 0·158 g of a solid which was identified as a ketone by the presence of an absorption peak at 1730 cm^{-1} in the infrared spectrum taken in chloroform solution. The compound was identified as 2:2-diphenyl*cyclo*pentanone by the preparation of the 2:4-dinitrophenylhydrazone, m.p. 180–181°; reported[25] 182–182·5°.

(Found: C, 66·46; H, 4·87; N, 13·19; Calc. for $C_{23}H_{20}N_4O_4$: C, 66·33; H, 4·84; N, 13·46%).

Numerous attempts were made to effect acid-catalyzed hydrolysis of the ketal in order to obtain the original 1:2-glycol. However, in every case either unchanged ketal or the rearrangement product, the ketone, was found.

Isolation of an ether from "anodic reduction" of 1:3-*dibenzoylpropane.* Following an electrolysis and work-up procedure of the type described under "anodic reduction" of 1:3-dibenzoylpropane, the chloroform solution remaining after an aliquot had been removed for lead tetraacetate titration was evaporated to dryness. The residue was subjected to fractional crystallization from absolute ethanol, and as one of the most soluble fractions there was obtained 0·070 g of a compound having an m.p. of 255·5–256·0° after two recrystallizations from acetone.

(Found: C, 83·29; H, 6·82; Calc. for $C_{34}H_{34}O_3$: C, 83·22; H, 6·98%).

The empirical formula of the compound strongly suggests that it is an ether derived from *cis*-1:2-diphenyl-1:2-*cyclo*pentanediol. It should be emphasized that this small amount of ether represents an anolyte product in addition to the parent 1:2-diol, which was obtained in 92% yield.

[25] N. R. Easton and S. J. Nelson, *J. Amer. Chem. Soc.* **75**, 640 (1953).

"*Anodic reduction*" *of* 1:4-*dibenzoylbutane*. Electrolyses in which 1:4-dibenzoylbutane was the organic additive were carried under the same conditions as described under "anodic reduction" of 1:3-dibenzoylpropane. The work-up of the anolyte after electrolysis was also identical, up to and including the point where the neutral fraction was isolated as solid.

The neutral solid was dissolved in freshly distilled acetone and made up to a volume of 100 ml. From this stock solution three 5-ml aliquots were withdrawn. Two of the aliquots were used for titration with standard lead tetraacetate solution. The third was evaporated to dryness, the residue dissolved in chloroform and the infrared spectrum taken.

In a series of three electrolyses in which the V_f values ranged from 1·52–1·60, the yields of 1:2-diol varied from 39·2 to 49·8 per cent. In each case the infrared spectrum indicated that products other than the diol had also been formed.

Following two electrolyses in which the V_f values were 1·52 and 1·60, the acetone solutions remaining after the aliquots noted above had been removed were combined and evaporated to dryness. The residue, which amounted to 4·34 g, was dissolved in 25 ml of hot petroleum ether (b.p. 38°) and the solution cooled and filtered. The precipitate which had formed was recrystallized from 25 ml of absolute methanol and there was obtained 1·97 g of starting diketone, m.p. 105–106°. The petroleum ether and methanol mother liquors were combined, evaporated to dryness, dissolved in anhydrous benzene, and chromatographed on 100 g of alumina. The column was developed with anhydrous benzene and adsorbed material eluted first with benzene and then with a 5% solution of methanol in benzene. Finally, the alumina was thoroughly extracted with methanol in a Soxhlet extractor.

Two products were obtained from the benzene eluant. The first compound to come through the column amounted to 1·18 g and had an m.p. of 42·4–43·4° after recrystallization from petroleum ether. This compound was identified as 1-benzoyl-2-phenyl-1-*cyclo*pentene(II) by means of a mixed melting point test with authentic II (see below), as well as by the identity of the infrared spectra taken in chloroform solution. The second product (0·43 g) was found to be starting diketone.

The third compound isolated, by elution with methanol-benzene, weighed 0·66 g. Following recrystallization from low boiling petroleum ether, the compound had an m.p. of 73·2–73·9°.

(Found: C, 80·31; H, 7·54; Calc. for $C_{18}H_{20}O_2$: C, 80·56; H, 7·51%).

This compound was identified as *cis*-1:2-diphenyl*cyclo*hexane-1:2-diol by the demonstration of the existence of intramolecular hydrogen bonding by the same method as employed with *cis*-1:2-diphen*cyclo*pentane-1:2-diol and by the preparation of the appropriate phenylboronate ester (see below).

Extraction of the alumina with methanol gave 0·08 g of a compound which was not identified but the infrared spectrum of which contained a peak at 1680 cm^{-1}, indicating the presence in the compound of a carbonyl group.

It is probable that a competing "anodic reduction" process, namely reduction of the water formed by intramolecular condensation of 1:4-dibenzoylbutane to give 1-benzoyl-2-phenyl-1-*cyclo*pentene, accounts for the relatively low yield of the diol.

Synthesis of 1-*benzoyl*-2-*phenyl*-1-cyclo*pentene*. To a solution of 13·3 g (0·05 mole) of 1:4-dibenzoylbutane in 200 ml of anhydrous benzene was added 3·9 g (0·1 mole) of sodium amide. The mixture was stirred for a few min at room temp and then heated

on a steam bath for 3 hr. About 150 g of ice was added, and the mixture permitted to stand overnight. The benzene layer was removed, washed with water, dried over anhydrous sodium sulfate, and the solvent removed by distillation. The residual oil was distilled at 1 mm press and the fraction of b.p. 155–164° was collected. When the oil was dissolved in hot low boiling petroleum ether and the solution allowed to cool, crystalline 1-benzoyl-2-phenyl-1-*cyclo*pentene was obtained and found to have an m.p. of 43·4–44·4°.

(Found: C, 86·91; H, 6·59; Calc. for $C_{18}H_{16}O$: C, 87·06; H, 6·49%).

The infrared spectrum of the compound in chloroform solution showed an absorption peak at 1645 cm^{-1} and was consistent in other respects with an α-β-unsaturated ketone structure.

cis-1:2-*Diphenyl*-1:2-cyclo*hexandiol phenylboronate.* To a solution of 50 mg of phenylboronic acid in 0·5 ml of absolute methanol was added 20 mg of the 1:2-diol, m.p., 73·2–73·9°. After the solution had been permitted to stand for several days at 0°, a white crystalline material precipitated. Its m.p. was 127–128° after recrystallization from absolute methanol.

(Found: C, 81·45; H, 6·61; B, 3·18: Calc. for $C_{24}H_{23}BO_2$: C, 81·37; H, 6·54; B, 3·05%).

Summary of yields of 1:2-*diols.* Although no attempts were made to isolate "anodic reduction" products of the diketones listed below, the following yields of 1:2-diols were determined by duplicate lead tetraacetate titrations:

Diketone	Yield of 1:2-diol%
1:2-dibenzoylethane	40
1:5-dibenzoylpentane	50
1:6-dibenzoylhexane	88
1:7-dibenzoylheptane	71
1:8-dibenzoyloctane	77

It should be emphasized that, owing to the relatively high V_i values (Fig. 1), the quantities of diols formed were very small and, therefore, the yields reported above are subject to relatively large errors.

"*Anodic reduction*" *of* 1:8-*dibenzoyloctane.* Following an electrolysis in which 1:8-dibenzoyloctane was present as additive and in which the theoretical yield of 1:2-diphenyl-1:2-*cyclo*decanediol was calculated to be 88 mg, the anolyte hydrolysate was worked up in the same manner as described for the 1:4-dibenzoylbutane electrolysis. The material eluted with methanol-benzene could not be crystallized, but the infrared spectrum of the material (in chloroform) indicated that the 1:2-diol had been concentrated in this fraction. The fact that there was absorption in the spectrum at both 3550 and 3590 cm^{-1} was consistent with the occurrence of hydrogen bonding.

Products formed at the cathode. It has already been shown that the cathodic reduction of benzil at a magnesium cathode in pyridine gives a quantitative yield of benzoin.[5] With diketones of the type in which two or more methylene groups separated the benzoyl groups attempts to isolate products from the catholyte hydrolysate gave highly colored, intractable material in every case. Titration of these materials with lead tetraacetate showed the presence of very small amounts of 1:2-diols (1–15%).

Corrosion experiments. Solutions of the diketones in sodium iodide-pyridine did not attack massive magnesium prior to electrolysis. However, in the two cases which were studied, namely with 1:3-dibenzoylpropane and benzil as additives, the anolyte solutions following electrolysis were capable of corroding the massive metal.

After an electrolysis in which 1:3-dibenzoylpropane was the additive and in which the V_i was 1·69, with 0·2752 g of magnesium entering solution from the anode, a freshly cleaned, weighed magnesium rod was placed in the anolyte. The rod was permitted to stand in the solution for a period of 123 hr, after which it was cleaned, dried and weighed. The loss in weight of the rod corresponded to the dissolution of 0·0071 g atom of magnesium. Inasmuch as the calculated quantity of radical-ion(III) ($n = 3$) produced during the electrochemical process was but 0·0035 g mole, it is evident[8] that corrosion occurred by a chain mechanism. The anolyte was hydrolyzed and worked up as described under "anodic reduction" of 1:3-dibenzoylpropane. The lead tetraacetate titration accounted for 70% of the *cis*-1:2-diphenyl-1:2-*cyclo*-pentanediol expected from a combination of electrolysis and corrosion by the chain mechanism described in the theoretical section. In a second corrosion experiment the pertinent data were: V_i, 1·71; loss of weight of anode during electrolysis, 0·1845 g; time of corrosion, 87 hr; loss in weight of magnesium rod during corrosion, 0·0073 g atom; calculated quantity of radical-ion produced during electrolysis, 0·0022 g mole; yield of diol as determined by lead tetraacetate titration, 73%. On the basis of calculations with the data from the second corrosion experiment, 6·6 times more magnesium was brought into solution in the corrosion process than would have been theoretically possible if the latter had occurred by the other than a chain mechanism.

Pertinent data for three corrosion experiments subsequent to electrolyses in which benzil was the additive follow: V_i, 1·48, 1·37, 1·62; loss of weight of anode during electrolysis, 0·4534, 0·5240, 0·1506 g; time of corrosion, 93, 336, 68 hr; loss in weight of magnesium rod during corrosion, 0·0131, 0·0106, 0·0115 g atom; calculated quantity of radical-ion (VI) produced during electrolysis, 0·0097, 0·0133, 0·0030 g mole. These data are definitely in accord with a chain mechanism for corrosion. Analysis of one of the reaction mixtures by the infrared method described previously[5] accounted for 81% of the benzoin expected from a combination of electrolysis and corrosion by the chain mechanism described in the theoretical section. Unlike the experiment with 1:3-dibenzoylbutane, there was a significant degree of corrosion of massive magnesium in the catholyte following electrolysis.

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RANEY NICKEL REDUCTIONS—VIII*

A SYNTHESIS OF 1:2-BENZANTHRACENE AND ITS 3'-METHYL AND 4-METHYL DERIVATIVES

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Abstract—1:2-Benzanthracene and the 3'-methyl derivative have been prepared by Raney nickel reduction of the sulphuric esters of the leuco derivatives of 1:2-benzanthraquinone and 4'-chloro-3'-methyl-1:2-benzanthraquinone, followed by dehydrogenation. 3-Hydroxy-1:2-benzanthraquinone was methylated in the 4-position by formaldehyde, sodium hydrosulphite and sodium hydroxide solution (the Marschalk reaction). Simultaneous reduction of the nuclear hydroxyl and quinone groups was effected by Raney nickel reduction of the trisulphuric ester of 3:9:10-trihydroxy-4-methyl-1:2-benzanthracene, and the resultant hexahydro-4-methyl-1:2-benzanthracene was dehydrogenated to 4-methyl-1:2-benzanthracene. The preparation of 3:4:9:10-dibenzopyrene from Mayvat brilliant red AF by Raney nickel reduction of the sulphuric ester of the leuco derivative and subsequent dehydrogenation is described.

THE action of Raney alloy and sodium hydroxide solution on the sulphuric ester of the leuco derivative is a general method[1] for the conversion of quinones to the corresponding hydrocarbon derivatives, which is a useful supplement to known methods such as zinc dust distillation and reduction by zinc, zinc chloride and sodium chloride.[2] Thus 3:4:8:9-dibenzopyrene can be readily prepared from the commercially available disodium salt (Indigosol golden yellow IGK) of the disulphuric ester of the leuco derivative of 3:4:8:9-dibenzopyrene-5:10-quinone (Indanthrene golden yellow GK); treatment with Raney alloy and sodium hydroxide solution gives a mixture of hydrogenated dibenzopyrenes, which is dehydrogenated to 3:4:8:9-dibenzopyrene by iodine and sodium acetate in boiling nitrobenzene.[1] This procedure was then employed for the synthesis of 1-azanaphthacene from 2-aminoanthraquinone via 1-azanaphthacene-6:11-quinone and the disulphuric ester of its leuco derivative.[3] 1:2-Benzanthracene derivatives and 3:4:9:10-dibenzopyrene, which are of interest in connexion with carcinogenic studies, have now been similarly prepared from the appropriate quinones.

The product obtained by heating the disodium salt of the disulphuric ester of 1:2-benzanthrahydroquinone with Raney alloy and sodium hydroxide solution was an octahydrobenzanthracene, dehydrogenation of which with 2:3-dichloro-5:6-dicyanobenzoquinone[4] or chloranil gave 1:2-benzanthracene; the overall yield from benzanthraquinone was 70 per cent. Benzanthracene was also obtained in similar yield by reduction of benzanthraquinone with aluminium tri*cyclo*hexoxide in *cyclo*hexanol.[5] Elbs prepared impure benzanthracene by reduction of the quinone with

* Part VII *J. Sci. Ind. Res.* **B15**, 279 (1956).
[1] N. B. Desai, V. Ramanathan, and K. Venkataraman, *J. Sci. Ind. Res.* **B14**, 330 (1955).
[2] E. Clar, *Ber. Dtsch. Chem. Ges.* **72**, 1645 (1939).
[3] N. B. Desai, V. Ramanathan and K. Venkataraman, *J. Sci. Ind. Res.* **B15**, 279 (1956).
[4] E. A. Braude, A. G. Brook and R. P. Linstead, *J. Chem. Soc.* 3569 (1954).
[5] S. Coffey and V. Boyd, *J. Chem. Soc.* 2468 (1954).

zinc and ammonia;[6] Badger and Cook[7,8] reduced the quinone successively with stannous chloride and acid to a resinous anthrol and then with zinc dust and sodium hydroxide to the hydrocarbon which required purification through the maleic anhydride adduct.

3′-Methyl-1:2-benzanthracene (I) was first synthesised by Cook[9] in 5–10 per cent yield by the pyrolysis of 1-benzoyl-2:6-dimethylnaphthalene, and subsequently by Newman and Gaertner[8] by a laborious process involving several steps. Hydrogenolysis of the disulphuric ester of the leuco derivative of 4′-chloro-3′-methyl-1:2-benzanthraquinone (II), followed by dehydrogenation, provides a much more convenient route to (I) in an overall yield of 40 per cent calculated on the phthalic anhydride used. 1-Chloro-2-methylnaphthalene condensed with phthalic anhydride in presence of aluminium chloride in the unsubstituted ring in the 6-position, as Scholl[10] has shown in the case of 2-chloro-1-methylnaphthalene, and cyclisation with sulphuric acid gave (II).

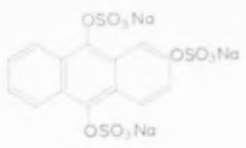
I

II

Since our projected synthesis of 4-methyl-1:2-benzanthracene (IV) involved the reduction of a β-hydroxyl group in an anthraquinone derivative, the reduction of 2-hydroxyanthraquinone to anthracene was first studied. The action of copper bronze on 2-hydroxyanthraquinone in chlorosulphonic acid and pyridine, followed by sodium hydroxide solution, gave a quantitative yield of the trisodium salt (III) of the trisulphuric ester of 2-hydroxyanthrahydroquinone. Treatment of (III) with Raney alloy and sodium hydroxide solution and dehydrogenation of the product with selenium gave anthracene in a yield of about 85 per cent. 3-Hydroxy-4-methylbenzanthraquinone (V) was then reduced to (IV) via the trisulphuric ester of the leuco derivative and dehydrogenation of the hexahydro-4-methylbenzanthracene obtained by hydrogenolysis with Raney alloy and alkali. For the preparation of (V) we used the Marschalk reaction,[11] condensing 3-hydroxybenzanthraquinone with formaldehyde and aqueous sodium hydroxide. An improvement in Fieser's procedure for the preparation of 3-hydroxybenzanthraquinone,[12] starting from 1-methoxynaphthalene and phthalic anhydride, is to oxidise 3-methoxy-1:2-benz-10-anthrone to 3-methoxybenzanthraquinone with sodium dichromate and acetic acid and demethylate with alumunium chloride–sodium chloride at 130–140°. The formation of (IV) by pyrolysis of 1-benzoyl-2:3-dimethylnaphthalene was first described by Fieser and Peters;[13] (IV) was synthesised later by Fieser and Jones[14,8] from 6-methyltetralin and phthalic anhydride. More recent syntheses of (IV) involve the

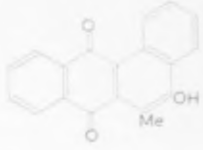
[6] K. Elbs, *Ber. Dtsch. Chem. Ges.* **19**, 2209 (1886).
[7] G. M. Badger and J. W. Cook, *J. Chem. Soc.* 802 (1939).
[8] M. S. Newman and V. R. Gaertner, *J. Amer. Chem. Soc.* **72**, 264 (1950).
[9] J. W. Cook, *J. Chem. Soc.* 456 (1932).
[10] R. Scholl, C. Seer and A. Zinke, *Monatshchrift* **41**, 583 (1921).
[11] C. Marschalk, *Bull. Soc. Chim.* **3**, 1545 (1936).
[12] L. F. Fieser and E. M. Dietz, *J. Amer. Chem. Soc.* **51**, 3141 (1929).
[13] L. F. Fieser and M. A. Peters, *J. Amer. Chem. Soc.* **54**, 3742 (1932).
[14] L. F. Fieser and R. N. Jones, *J. Amer. Chem. Soc.* **60**, 1940 (1938).

condensation of 9-methyl-1:2:3:4-tetrahydrophenanthrene with succinic anhydride[15] and the condensation of 2-allyl*cyclo*hexanone with tetralin.[16] The present procedure utilises more readily available intermediates; it is also applicable to the synthesis of other 4-alkylbenzanthracenes.



III

IV



V

The preparation of the potent carcinogen, 3:4:9:10-dibenzopyrene, from the 5:8-quinone by reduction with aluminium tri*cyclo*hexoxide[5] was described in a recent communication.[17] An alternative and equally convenient method is to convert Mayvat brilliant red AF, which is mainly a dibromo-3:4:9:10-dibenzopyrene-5:8-quinone, into the sulphuric ester of the leuco derivative, reduce this ester with Raney alloy and sodium hydroxide solution, and dehydrogenate the mixture of hydrogenated hydrocarbons thus obtained with selenium.

EXPERIMENTAL

Hydrogenolysis of the disodium salt (VI) *of the disulphuric ester of benzanthrahydroquinone.* Chlorosulphonic acid (5 ml) was slowly run into pyridine (50 ml) below 20°. The mixture was heated to 60°, 1:2-benzanthraquinone (5 g) was added, followed by an equal weight of copper bronze. After stirring at 60–65° for 3 hr, the mixture was poured into 150 ml of 10% NaOH solution and filtered from copper. From the filtrate, pyridine was removed by steam distillation, the residue was cooled, just acidified (Congo Red) with HCl, and filtered. The filtrate, which exhibited a violet fluorescence on dilution, contained the theoretical amount of (VI), as determined by ceric sulphate oxidation.[18] An aliquot part of this solution, containing 6·2 g of (VI), corresponding to 3·5 g of the quinone, was made up to 620 ml, and sodium hydroxide (62 g) added. The alkaline solution was heated on a boiling water-bath and Raney alloy (62 g) added in the course of 2 hr. After stirring for 2 hr more, the mixture was cooled, filtered, the nickel residue deactivated with HCl and extracted with alcohol. Removal of the solvent gave 2·7 g of a pale yellow viscous oil, b.p. 175–8°/0·7 mm (Found: C, 91·3; H, 8·3. $C_{18}H_{20}$ requires: C, 91·5; H, 8·5%).

1:2-*Benzanthracene.* The above hydrogenated hydrocarbon (1 g) was dissolved in benzene (25 ml), 2:3-dichloro-5:6-dicyanobenzoquinone (5 g) in 50 ml benzene was added, and the mixture refluxed for 2 hr. After dilution with petroleum ether, the precipitated quinol was filtered and the filtrate run through a short column of alumina. The colourless percolate, which had a blue fluorescence, on removal of the solvent, gave the aromatic hydrocarbon, which crystallised from alcohol in shining leaflets (0·9 g), m.p. 159° (Found: C, 94·6; H, 5·3. $C_{18}H_{12}$ requires: C, 94·7; H, 5·3%). The m.p. quoted in the literature[2] is 158–159°.

Reduction of 1:2-*benzanthraquinone with aluminium tri*cyclo*hexoxide.* 1:2-Benzanthraquinone (1 g) was refluxed with a solution of aluminium (1 g) in *cyclo*hexanol (20 ml) for 40 hr. The solvent was distilled off, the residue poured into 3% NaOH solution, and filtered. The alkali-insoluble residue was extracted with alcohol. The alcohol extract, on concentration and cooling, gave pale yellow plates (0·7 g), m.p. 151–2°. Recrystallisation from alcohol gave almost colourless, shining plates, m.p. 159°, undepressed when mixed with 1:2-benzanthracene obtained in the previous experiment.

2-(5′-*Chloro*-6′-*methyl*-2′-*naphthoyl*)*benzoic acid.* To a clear solution of phthalic anhydride

[15] W. E. Bachman, M. W. Cronyn and W. S. Struve, *J. Org. Chem.* **12,** 596 (1947).
[16] O. P. Vig, S. V. Kessar and S. M. Mukherji, *Nature, Lond.* **174,** 834 (1954).
[17] B. D. Tilak, M. K. Unni and K. Venkataraman, *Tetrahedron* **3,** 62 (1958).
[18] K. Venkataraman, *The Chemistry of Synthetic Dyes* Vol. II, p. 1058. Academic Press, New York (1952).

(8·5 g) and 1-chloro-2-methylnaphthalene (9·8 g) in acetylene tetrachloride (50 ml) was added anhydrous aluminium chloride (15 g) in four lots in 1 hr at room temp. The mixture was stirred for 8 hr, left overnight, poured into ice-cold HCl, and the solvent removed by steam distillation. The resinous residue was washed with water, dissolved in Na_2CO_3 solution and reprecipitated with acid, when the keto acid was obtained as a granular mass (16 g), m.p. 90–100° after softening at 60°. The substance was uncrystallisable, but cyclisation yielded a readily crystallisable anthraquinone derivative. When the acid was purified by running the dark brown solution in benzene through a short column of Florex, recovering the pale yellow product from the percolate, diluting the alcoholic solution with water, and letting stand in a refrigerator for a few days; it was obtained as a buff coloured powder, melting indefinitely at about 120° (Found: C, 70·1; H, 4·6; Cl, 9·4. $C_{19}H_{13}O_3Cl$ requires: C, 70·4; H, 4·0; Cl, 11·0%). Fieser and Peters[12] encountered similar difficulty in crystallising the condensation products of phthalic anhydride and methylnaphthalenes.

4′-Chloro-3′-methylbenzanthraquinone (II). A solution of 2-(5′-chloro-6′-methyl-2′-naphthoyl)-benzoic acid (10 g) and boric acid (10 g) in conc. H_2SO_4 (100 ml) was stirred at 60–70° for 4 hr. On pouring into water the greenish yellow precipitate was filtered, washed with dilute NaOH solution and dried (6·5 g). It crystallised from benzene in elongated yellow needles, m.p. 227° (Found: C, 74·4; H, 3·5; Cl, 11·2. $C_{19}H_{11}O_2Cl$ requires: C, 74·3; H, 3·6; Cl, 11·6%).

Disodium salt of the disulphuric ester of 4′-chloro-3′-methylbenzanthrahydroquinone. The reduction and esterification were carried out as in the case of benzanthraquinone; 6·5 g of the quinone (II) gave a solution containing 8·7 g of the disodium salt of the ester (80% yield), as determined by the ceric sulphate method.[18]

Hydrogenolysis of the disodium salt of the disulphuric ester of 4′-chloro-3′-methylbenzanthrahydroquinone. A solution containing the ester (8 g) was made up to 800 ml and sodium hydroxide (80 g) added. The alkaline solution was heated on a water-bath and Raney alloy (80 g) added in 2 hr. After stirring for 3 hr more, the mixture was cooled and filtered, and the nickel residue, after deactivation with acid, extracted with alcohol. The alcohol extract yielded 3·6 g of a viscous oil, b.p. 205–10°/2 mm (Found: C, 91·8; H, 8·3. $C_{19}H_{20}$ repuires: C, 91·9; H, 8·1%).

3′-Methyl-1:2-benzanthracene (I). A mixture of the hydrogenated hydrocarbon (2 g) and 2:3-dichloro-5:6-dicyanobenzoquinone (7·5 g) was refluxed with benzene (100 ml) for 2 hr. The precipitated quinol was filtered off and the filtrate run through a short column of alumina. The pale yellow percolate on removal of the solvent gave yellow plates, which crystallised from alcohol in shining pale yellow plates (1·75 g), m.p. 160° (Found: C, 93·8; H, 6·1. $C_{19}H_{14}$ requires: C, 94·2; H, 5·8%). The picrate crystallised from alcohol in red needles, m.p. 144°. Cook[9] quotes m.p. 160° for the hydrocarbon and 144–45° for the picrate.

Hydrogenolysis of the trisodium salt of the trisulphuric ester of 2-hydroxyanthrahydroquinone. Chlorosulphonic acid (6·5 ml) was slowly run into a mixture of 2-hydroxyanthraquinone (5 g) and pyridine (60 ml) below 20°. After stirring the paste at 20° for 30 min, the temp. was raised to 60° and copper bronze (5 g) added. Stirring was continued at this temp. for 3 hr, the reaction mixture then poured into 10% NaOH solution (250 ml) and filtered. From the filtrate pyridine was removed by steam distillation and the solution filtered again to remove the precipitated impurities. The filtrate was made up to 1100 ml, made alkaline with 110 g NaOH, and heated on a water-bath with Raney alloy (110 g) added in the course of 2 hr. After heating for a further 2 hr, the mixture was filtered, the nickel residue deactivated with acid and extracted with alcohol. The alcohol extract on removal of solvent gave a colourless product (3·3 g) which crystallised from aqueous acetic acid in colourless plates, m.p. 93° (Found: C, 92·1; H, 8·0. $C_{14}H_{14}$ requires: C, 92·3; H, 7·7%). The tetrahydroanthracene (3 g) was mixed with selenium (10 g) and heated to 300° gradually. The product was extracted with alcohol leading to colourless plates (2·7 g), m.p. 216°, undepressed when mixed with anthracene.

3-Methoxy-1:2-benzanthraquinone. 3-Methoxy-1:2-benz-10-anthrone was prepared according to Fieser and Dietz, starting from 1-methoxynaphthalene and phthalic anhydride.[12] The anthrone (40 g) was suspended in glacial acetic acid (200 ml) and treated with sodium dichromate (40 g) dissolved in water (20 ml). The mixture was stirred on a water-bath for 15 min, during which the reaction mixture boiled vigorously. Dilution with cold water gave a bright orange-brown precipitate of the quinone (33 g). Crystallisation from benzene gave brown needles, m.p. 188° (Fieser and Dietz, m.p. 188·5°).

3-Hydroxy-1:2-benzanthraquinone. An intimate mixture of aluminium chloride (50 g) and sodium

chloride (10 g) was melted on a free flame. 3-Methoxybenzanthraquinone (10 g) was quickly added to the melt and the mixture stirred with a thermometer at 140–45° for 2 min. The melt was poured into ice-cold 5% HCl, when the hydroxy compound separated as an orange-brown precipitate (9·5 g). The product dissolved in alkali with a deep purple colour, which changed to orange-red on adding sodium hydrosulphite. The acetyl derivative, prepared by refluxing with acetic anhydride and a drop of H_2SO_4, crystallised from benzene in stout yellow needles, m.p. 232° (Fieser and Dietz, m.p. 232°). The acetyl derivative was hydrolysed by dissolving in cold conc. H_2SO_4 and pouring into water. The hydroxy compound crystallised from dioxane in orange-red plates, decomposing at about 250° (Found: C, 78·6; H, 3·8. $C_{18}H_{10}O_3$ requires: C, 78·8; H, 3·7%). Fieser and Dietz have not recorded the m.p. or analysis of this compound.

3-*Hydroxy*-4-*methyl*-1:2-*benzanthraquinone* (V). 3-Hydroxybenzanthraquinone (6 g) was dissolved in NaOH solution (600 ml) and vatted with 15 g of sodium hydrosulphite at 40–45° for 10 min in a nitrogen atmosphere. The solution was treated with 37·5% formalin (4·2 ml) and stirred on a water-bath for 1 hr. The mixture was cooled and air-oxidised; acidification gave an orange-brown precipitate (4·8 g). The acetyl derivative crystallised from benzene-hexane in thin yellow needles, m.p. 203° (Found: C, 76·7; H, 4·1. $C_{21}H_{14}O_4$ requires: C, 76·4; H, 4·3%). The methyl ether, prepared by the action of dimethyl sulphate and NaOH solution, crystallised from alcohol in thin yellow needles, m.p. 146° (Found: C, 79·3; H, 4·5. $C_{20}H_{14}O_3$ requires: C, 79·5; H, 4·6%). The acetyl derivative was hydrolysed by cold conc. H_2SO_4; the hydroxy compound (V) crystallised from dioxane in orange-brown platelets, m.p. 228° (Found: C, 79·1; H, 4·4. $C_{19}H_{12}O_3$ requires: C, 79·2; H, 4·2%).

Hydrogenolysis of the trisodium salt of the trisulphuric ester of 3-*hydroxy*-4-*methylbenzanthrahydroquinone*. Chlorosulphonic acid (6 ml) was slowly run into a mixture of 3-hydroxy-4-methylbenzanthraquinone (V, 5 g) and pyridine (50 ml) below 20°. The paste was stirred at 20° for 30 min, the temp. then raised to 60° and copper bronze (5 g) added. After stirring the mixture at this temp. for 3 hr, it was poured into 200 ml of 10% NaOH solution and filtered. The filtrate, after removal of pyridine, was cooled, just acidified and filtered from brown impurities. The filtrate, which was almost colourless with a blue fluorescence, was used for hydrogenolysis. The solution was made up to 1040 ml, and heated at 70° with sodium hydroxide (104 g) and Raney alloy (104 g) gradually added during 3 hr. The mixture was then stirred on a boiling water-bath for 3 hr, cooled and filtered. The nickel residue was deactivated with dilute HCl and extracted with alcohol. The brown viscous oil, obtained after the removal of alcohol, was dissolved in hexane and run through a short column of alumina. The colourless percolate on removal of solvent gave an almost colourless oil (3·2 g), b.p. 205–8°/2 mm (Found: C, 91·9; H, 8·1. $C_{19}H_{20}$ requires: C, 91·9; H, 8·1%).

4-*Methyl*-1:2-*benzanthracene* (IV). The hydrogenated hydrocarbon (0·44 g), 2:3-dichloro-5:6-dicyanobenzoquinone (0·6 g) and benzene (40 ml) were refluxed for 30 min. More quinone (0·6 g) was added, the mixture refluxed for 2 hr, filtered, and the brown filtrate run through a short column of alumina. The clear yellow percolate on removal of solvent gave a brown oil, which was dissolved in alcohol. The alcoholic solution was concentrated and treated with picric acid. On cooling red-brown needles of the picrate crystallised. After two crystallisations from the same solvent it melted at 148° (Found: C, 64·2; H, 3·6; N, 9·2. $C_{25}H_{17}N_3O_7$ requires: C, 63·7; H, 3·6; N, 8·9%). The picrate was decomposed with dilute ammonia and the hydrocarbon crystallised from alcohol containing a little benzene; the colourless needles had m.p. 124° (Found: C, 94·0; H, 6·2. $C_{19}H_{14}$ requires: C, 94·2; H, 5·8%). Fieser and Jones[14] cite m.p. 124–124·6°.

Sulphuric ester of the leuco derivative of Mavat brilliant red AF. Chlorosulphonic acid (5 ml) was slowly run into pyridine (50 ml) below 20°. The temp. was then raised to 50° and the finely divided dye (5 g) added to it, followed by copper bronze (5 g). After stirring the mixture at 60–65° for 3 hr, it was poured into 200 ml of water containing 20 g NaOH and filtered. The solution obtained after the removal of pyridine by steam distillation of the filtrate contained ester corresponding to 4·5 g of the dye. The estimation was carried out by oxidising an aliquot part with ceric sulphate and weighing the precipitated dye.[10]

Reduction of the sulphuric ester of the leuco derivative of Mavat brilliant red AF. The solution containing ester (sodium salt) corresponding to 3·0 g of the dye was made up to 500 ml and sodium hydroxide (50 g) added. The alkaline solution was heated on a water-bath and Raney alloy (50 g) added in the course of 2 hr. After stirring for 2 hr more, the reaction mixture was filtered. The nickel was deactivated and extracted with benzene. The benzene extract, after running through a

short column of alumina, gave on concentration and cooling pale yellow plates (1·4 g). The product (1 g) was dissolved in hexane and chromatographed on alumina. The chromatogram was developed and eluted with hexane–benzene mixture. The first fraction, colourless with a faint blue fluorescence, gave colourless needles (0·16 g), m.p. 175° (Found: C, 93·5; H, 7·1. $C_{24}H_{22}$ requires: C, 92·9; H, 7·1%). The second fraction, colourless with a blue fluorescence, gave colourless shining plates (0·76 g), m.p. 223° (Found: 93·8; H, 5·7. $C_{24}H_{18}$ requires: C, 94·1; H, 5·9%). The product (0·6 g) was mixed with selenium (1·2 g) and heated at 290–300° for 3 hr. The mass was cooled and extracted with benzene. The benzene extract, after running through a short column of alumina, led to shining yellow plates (0·45 g), m.p. 281° (Found: C, 94·9; H, 4·7. $C_{24}H_{14}$ requires: C, 95·3; H, 4·7%). Identity with 3:4:9:10-dibenzopyrene was proved by its absorption spectrum and mixed m.p. with the hydrocarbon obtained by the reduction of 3:4:9:10-dibenzopyrene-5:8-quinone with aluminium *tricyclo*hexoxide.[17]

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STUDIES ON THE BIOSYNTHESIS OF CHOLESTEROL—7*

REARRANGEMENT OF METHYL GROUPS DURING ENZYMIC CYCLISATION OF SQUALENE

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Abstract—The present state of knowledge of the biosynthesis of cholesterol is summarised. An experiment is described wherein a special application of the carbon isotope ^{13}C permits a decision between possible modes of rearrangement during the enzymic cyclisation of squalene.

INTRODUCTION

As knowledge is acquired of the manner in which an animal cell synthesises cholesterol, it becomes evident that this sterol, and indeed steroids as a class, belong biogenetically to a much larger family which also includes terpenoids and carotenoids. This family might be termed the *polyprenoids*, since they seem to be built up by association of units each of which contributes a branched chain of five carbon atoms at the oxidation level of isoprene.

Except for the fact that it undoubtedly was synthesised in the animal body, nothing was known for certain about the biosynthesis of cholesterol until isotopically labelled precursors were used. The discovery[1] that deuterioacetic acid is efficiently incorporated by yeast cells into unsaponifiable lipids (mainly ergosterol) was soon followed by demonstrations[2] that acetic acid is an important source of carbon for cholesterol. Konrad Bloch's pioneering work[3] established that acetic acid molecules are incorporated into the structure of cholesterol according to a definite pattern, and this pattern has been completely elucidated[4–9] by the total degradation of cholesterol biosynthesised from radioactive acetic acid, each of the twenty-seven carbon atoms in the structure being identified as coming from the methyl group or from the carboxyl group of acetic acid. The pattern is shown in (I) (*m* = "methyl carbon",

* Part 6: *Biochem. J.* **69,** 238 (1958). A preliminary account of the present work has already appeared: *Proc. Chem. Soc.* 112 (1958).

[1] R. Sonderhoff and H. Thomas, *Liebigs Ann.* **530,** 195 (1937).
[2] K. Bloch and D. Rittenberg, *J. Biol. Chem.* **159,** 45 (1945); K. Bloch, E. Borek and D. Rittenberg, *J. Biol. Chem.* **162,** 441 (1946).
[3] H. N. Little and K. Bloch, *J. Biol. Chem.* **183,** 33 (1950).
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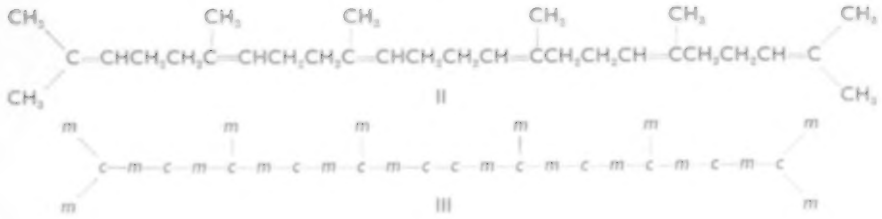
[9] J. W. Cornforth, I. Youhotsky Gore and G. Popják, *Biochem. J.* **65,** 94 (1957).

c = "carboxyl carbon"). The work was greatly facilitated by the use of slices or cell-free extracts of rat liver to prepare cholesterol from radioactive precursors.

I



II

III

V IV

The pattern in the side-chain, which was elucidated first, was related by Bloch to a theory[10] of biosynthesis of the rubber hydrocarbon from acetic acid: and this suggestion of a common origin for terpenes and sterols led him to revive an old hypothesis to which Heilbron,[11] Channon[12] and Robinson[13] had contributed: that squalene (II) might be a precursor of cholesterol. Bloch then demonstrated[14] that squalene is indeed produced from acetic acid, and is converted into cholesterol, in the animal body. By total degradation of squalene biosynthesised from acetic acid we discerned[15] the pattern (III) of "methyl" and "carboxyl" carbons.

The next correlation was made when the structure of lanosterol (IV) suggested to Woodward and Bloch[6] that this substance might be an intermediate between squalene and cholesterol. The hypothesis required that the squalene molecule should be folded for cyclisation in a manner (V) differing from that proposed[13] earlier; and rearrangement of at least one methyl group during cyclisation was a necessary consequence.

[10] J. Bonner and B. Arreguin, *Arch. Biochem. Biophys.* **21**, 109 (1949).
[11] I. M. Heilbron, E. D. Kamm and W. M. Owens, *J. Chem. Soc.* 1630 (1926).
[12] H. J. Channon, *Biochem. J.* **20**, 400 (1926).
[13] R. Robinson, *J. Soc. Chem. Ind.* **51**, 464 (1932).
[14] R. G. Langdon and K. Bloch, *J. Biol. Chem.* **200**, 129, 135 (1953).
[15] J. W. Cornforth and G. Popják, *Biochem. J.* **58**, 403 (1954).

The pattern (I) of "methyl" and "carboxyl" carbons is completely in harmony with the pattern (III) in squalene when this mode of cyclisation is assumed. Moreover, labelling technique enabled Bloch to show[16,17] that squalene is indeed converted biosynthetically into lanosterol, and lanosterol into cholesterol. Knowledge of the intermediate stages (perhaps ten to twelve in number) between lanosterol and cholesterol is growing rapidly and a complete account may soon be available of the order and manner in which the three superfluous methyl groups are (oxidatively) eliminated and the change from an 8:24-diene to a 5-ene is effected.

The stages of biosynthesis between acetic acid and squalene are less well understood and several gaps remain to be filled; but an important advance was made when mevalonic acid (VI), a growth factor for *Lactobacilli*,[18,19] was discovered[20] to be a highly efficient precursor of cholesterol. When mevalonic acid is incubated with rat-liver homogenate under nitrogen squalene rather than cholesterol is formed,[21] and when squalene biosynthesised in this way from 2-^{14}C-mevalonic acid is degraded,[21,22] radioactive carbon is found at only six positions in the molecule (VII).

VI

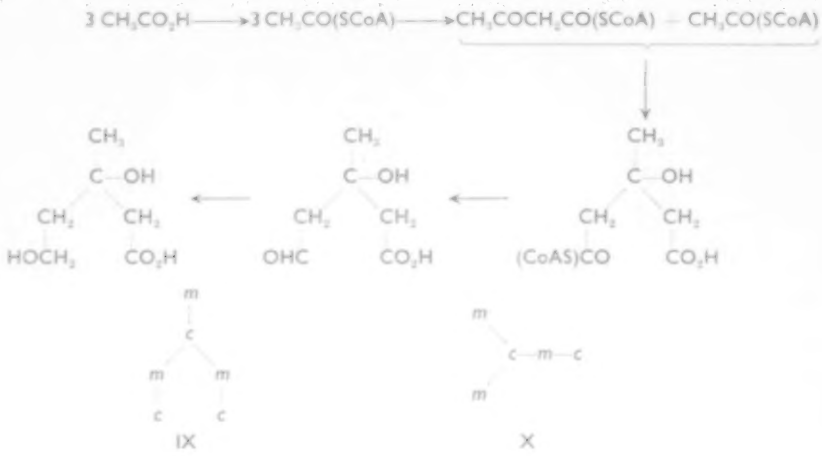
VIII

VII

The presumption that the C_{30} squalene (and hence cholesterol) is built up of six C_5 units, each contributed by one molecule of mevalonic acid, is well supported by other evidence: the carboxyl group of mevalonic acid is totally lost as carbon dioxide during biosynthesis of cholesterol;[23] mevalonic acid labelled at position 2 with ^{14}C and at position 5 with tritium is incorporated into squalene without change of the ^{14}C : T ratio;[24] and cholesterol biosynthesised from 2-^{14}C-mevalonic acid has been shown[25] to carry radioactive carbon at five positions only, of which three were identified and found to correspond with the predicted labelling illustrated in (VIII).

[16] R. B. Clayton and K. Bloch, *J. Biol. Chem.* **218**, 305, 319 (1956).
[17] T. T. Tchen and K. Bloch, *J. Biol. Chem.* **226**, 921 (1957).
[18] L. D. Wright, E. L. Cresson, H. R. Skeggs, G. D. E. MacRae, C. H. Hoffman, D. E. Wolf and K. Folkers, *J. Amer. Chem. Soc.* **78**, 5273 (1956).
[19] D. E. Wolf, C. H. Hoffman, P. E. Aldrich, H. R. Skeggs, L. D. Wright and K. Folkers, *J. Amer. Chem. Soc.* **78**, 4499 (1956).
[20] P. A. Tavormina, M. H. Gibbs and J. W. Huff, *J. Amer. Chem. Soc.* **78**, 4498 (1956).
[21] J. W. Cornforth, R. H. Cornforth, G. Popják and I. Youhotsky Gore, *Biochem. J.* **66**, 10P (1957); **69**, 146 (1958).
[22] F. Dituri, S. Gurin and J. L. Rabinowitz, *J. Amer. Chem. Soc.* **79**, 2650 (1957).
[23] P. A. Tavormina and M. H. Gibbs, *J. Amer. Chem. Soc.* **78**, 6210 (1956).
[24] B. H. Amdur, H. Rilling and K. Bloch, *J. Amer. Chem. Soc.* **79**, 2647 (1957).
[25] O. Isler, R. Rüegg, J. Würsch, K. F. Gey and A. Pletscher, *Helv. Chim. Acta* **40**, 2369 (1957).

The connexion between acetic acid and mevalonic acid is still being established, but the most probable sequence is



This would make the arrangement of acetic acid "methyl" and "carboxyl" carbons in mevalonic acid as shown in (IX). Consequently the C_5 unit, six of which go to make squalene, is (X) in terms of "methyl" and "carboxyl" carbons, and the pattern in squalene formed by association of these units is identical with that found by experiment. Several research groups are studying the role of mevalonic acid as a precursor of other polyprenoids,[26–28] and the evidence is already strong that in mevalonic acid or a closely related substance we have the basis of the "isoprene rule" (mevalonic acid $- CO_2 - 2H_2O =$ isoprene!), though it is still uncertain whether decarboxylation of the acid necessarily precedes the association of units.

THE CYCLISATION OF SQUALENE

The biogenetic relation of squalene with lanosterol led Ruzicka's school to formulate detailed schemes of biogenesis[29] whereby the carbon skeletons of all known types of triterpenoids could be derived from squalene. All cyclisations and rearrangements were pictured as carbonium-ion reactions, and a few simple and well-founded assumptions were made about the stereochemical course of these changes. The condition was also accepted that each sequence should be "non-stop": once a carbonium ion had been generated in squalene by attack of a cation, the positive charge was not expelled or neutralised except to form the final product. This idea that squalene is cyclised non-stop to lanosterol was strongly supported by the finding[30] that lanosterol biosynthesised from squalene in a heavy water medium contained no excess deuterium attached to carbon. The assumption that a cationic species like ^+OH initiated the cyclisation was also supported: experiments with ^{18}O showed that the oxygen atom of lanosterol is supplied by molecular oxygen, not by water.

[26] G. D. Braithwaite and T. W. Goodwin, *Biochem. J.* **67**, 13P (1957).
[27] D. Arigoni, *Experientia* **14**, 153 (1958).
[28] A. J. Birch, R. W. Rickards and H. Smith, *Proc. Chem. Soc.* 192 (1958).
[29] A. Eschenmoser, L. Ruzicka, O. Jeger and D. Arigoni, *Helv. Chim. Acta* **38**, 1890 (1955).
[30] T. T. Tchen and K. Bloch, *J. Biol. Chem.* **226**, 931 (1957).

In the proposed mechanism, an hydroxyl cation attacks a terminal double bond in squalene, initiating a concerted reaction which successively closes rings A, B and C. The stereochemistry of lanosterol requires that closure of ring D be accompanied by rearrangements of carbonium ions for which the original paper should be consulted.* Disregarding this refinement, the cyclisation can be pictured as (XI → XII). A series of 1 : 2-shifts, executed by two hydrogen atoms and two methyl groups and ended by expulsion of a proton from $C_{(9)}$, completes the synthesis of lanosterol (XIII → XIV).

XI XII

XIII XIV

To an organic chemist, this scheme is most attractive, for 1 : 2-shifts and cationic cyclisation of dienes are familiar to him. However, 1 : 3-shifts are also not unknown, and the Swiss authors explicitly recognised that the methyl group marked A in (XIII) might move directly to $C_{(13)}$ of lanosterol instead of replacing methyl group B on $C_{(14)}$. Also, it is not *a priori* impossible that a series of squalene molecules might be so arranged upon an enzyme surface that transfer or exchange of methyl groups occurred—an intermolecular rearrangement.

It seemed to us, then, that a valuable experimental test of current theories of biogenesis of cyclic polyprenoids, as well as a contribution to the specific problem of cholesterol biosynthesis, could be made by determining whether a double intramolecular 1 : 2-shift of methyl groups occurs during cyclisation of squalene to lanosterol, or whether the necessary rearrangement takes place by a 1 : 3-shift or by intermolecular transfer. Since the first mechanism is chemically the most plausible, we were inclined to arrange the experiment so that the results would distinguish sharply between this mechanism and the other two. A different procedure would have been required to distinguish between the second and third.

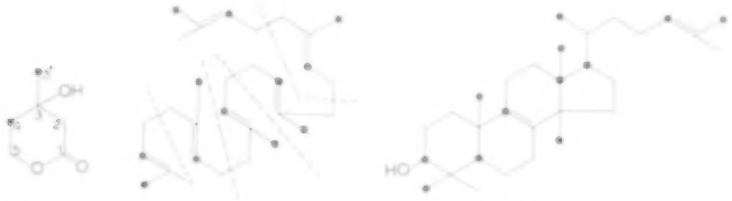
THE EXPERIMENTAL APPROACH

It might appear that the problem could be resolved fairly easily by labelling the appropriate methyl group in squalene, but this is not so. Squalene is a symmetrical molecule; groups A and B are identical in (XI); neither can be labelled without

* If the double bond marked * in squalene (XI) were isomerised to *cis* geometry before cyclisation, a much more direct cyclisation could be formulated.

effectively labelling the other. A more refined approach is to label both the methyl-group carbon and the carbon atom to which, during cyclisation, it is supposed to migrate; and then to separate from the product (lanosterol or cholesterol) a degradation product containing both these atoms. However, the symmetry of squalene will defeat even this attempt to distinguish between the three mechanisms, so long as the final measurement of isotopic content is expressed as the average for a large number of molecules. Only if it were possible to examine the isotopic content of individual molecules of the degradation product, that is, to count the molecules having two isotopic atoms and those having one and none, could the labelling be so arranged that the mechanisms were distinguishable. This reasoning led to the experiment now to be described. The discovery of mevalonic acid as a precursor of squalene and cholesterol enabled us to replace by a simpler procedure our first schemes requiring a synthesis of squalene.

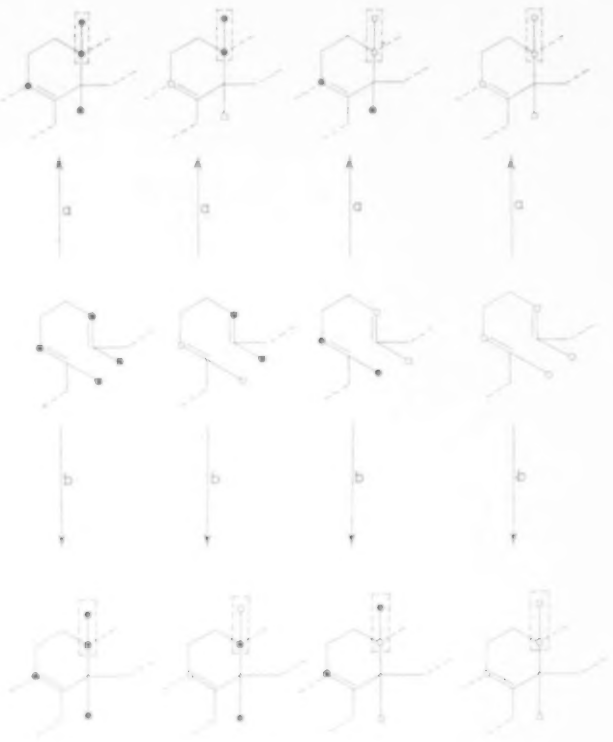
The principle of the experiment can be illustrated by an ideal example. Imagine a specimen of mevalonolactone (XV), which is equivalent to the acid in biosynthesis, having 100% ^{13}C at positions 3′ and 4, and 100% ^{12}C elsewhere. Let this mevalonolactone be converted biosynthetically into squalene (XVI). Each squalene molecule will contain twelve ^{13}C atoms occupying the positions indicated; the division into C_5 units is shown by broken lines. When this squalene is converted into lanosterol, the twelve ^{13}C atoms occupy the positions shown in (XVII), irrespective of the mechanism of cyclisation.



(XV) (XVI) (XVII)

Now suppose that before biosynthesis the mevalonolactone is diluted by an equal number of molecules of lactone containing only ^{12}C. Many isotopic types of squalene will be formed, but for the present purpose only the two central C_5 units are significant. One-quarter of all squalene molecules would have two labelled units at the central positions; one-quarter would have two unlabelled units; and the remaining half would have one unit of each type. When the squalene is adsorbed on the enzyme surface for cyclisation, the non-symmetric type can be oriented in two equally probable ways, so that the cyclisation occurs with equal numbers of the four types shown on the middle line of scheme 1. If cyclisation is accompanied by a double 1 : 2-shift—mechanism (a)—the four types of lanosterol produced will be as shown on the upper line of Scheme 1; if there is a single 1 : 3-shift—mechanism (b)—the four types on the lower line of Scheme 1 will be formed. The C_2 fragment enclosed by broken lines in Scheme 1, when separated from the lanosterol or from the cholesterol derived from it, will be found to contain equal numbers of doubly-isotopic and non-isotopic molecules if mechanism (a) is correct; but by mechanism (b) half the molecules are singly-isotopic and one-quarter each are doubly-isotopic and non-isotopic. If the methyl group is transferred intermolecularly, the distribution is the same as for

mechanism (b). The significant difference between (a) and (b) is that (a) is a migration within a single C_5 unit, and no dilution with non-isotopic mevalonolactone can change the certainty of a ^{13}C atom becoming attached to another ^{13}C atom after migration; but when migration is between different units, the chance of two ^{13}C



Scheme 1

atoms becoming connected diminishes with the dilution. However, it is still true that if the isotopic content of the C_2 fragment were determined in the usual way by combustion and measurement of CO_2, the answer (50% ^{13}C) would be the same for (a) and (b). This would also be true if the isotope were ^{14}C and the radioactivity of the fragment had been measured. Therefore, it would be necessary to examine the C_2 fragment or a suitable derivative in a mass spectrometer, since this instrument can separate molecules differing in mass and could measure directly the proportions of doubly-isotopic, singly-isotopic and non-isotopic molecules.

The experiment as formulated above would be too difficult in practice. Homogeneous ^{13}C is not available; normal carbon contains 1·1% ^{13}C; the biosynthesis cannot yet be done without dilution of the isotopic material by endogenous end-products or intermediates; and the actual separation of a C_2 fragment containing $C_{(13)}$ and $C_{(18)}$ of cholesterol, although it has been done,[9] requires more material than could easily be made. However, it is possible to obtain the same information by less

exacting procedures; and in the experiment as planned, four stages were proposed:

(1) To make mevalonolactone containing a large excess of ^{13}C at positions 3′ and 4 (and nowhere else), and to dilute it with a comparable amount of normal mevalonolactone.

(2) To obtain biosynthetic cholesterol, diluted as little as possible with endogenous material, by incubating this mevalonolactone with preparations of rat liver.

(3) To oxidise this cholesterol to acetic acid, and to determine the proportion of acetic acid molecules containing $C_{(18)} + C_{(13)}$ of cholesterol.

(4) To measure this acetic acid by mass spectrometry to obtain the proportions of doubly-isotopic, singly-isotopic and non-isotopic molecules.

PREPARATION OF LABELLED MEVALONOLACTONES

Two new syntheses of mevalonolactone were devised, the first to obtain ^{13}C-labelled material for the main experiment and the second to prepare 4-^{14}C-mevalonolactone which was required for some confirmatory experiments.

The starting-point for the first synthesis (Scheme 2), ^{13}C-potassium cyanide, was converted[31] into 2-^{13}C-acetic acid (XVIII) and thence to acetyl chloride. An ethereal solution of diketen (XIX), obtained[32] by the action of triethylamine on this acetyl chloride in ether, was added to lithium aluminium hydride, when 2:4-$^{13}C_2$-3-oxobutanol (XX) was formed. An analogous reduction of *cyclo*hexylketen dimer had previously[33] been reported. The 3-oxobutanol was acetylated by keten to 2 : 4-$^{13}C_2$-3-oxobutyl acetate (XXI). Dilution, with a slightly larger amount of normal material, was done for convenience at this stage rather than with mevalonolactone. The diluted product was now treated with keten in the presence of boron trifluoride, and the intermediate product (presumably the β-lactone (XXII)) was saponified. Acidification, distillation and further purification then gave crystalline 3′:4-$^{13}C_2$-mevalonolactone (XXIII). Normal mevalonolactone can be conveniently prepared in quantity by this method, using 3-oxobutyl acetate prepared from methyl vinyl ketone.

Scheme 2

The isotopic composition of this mevalonolactone follows from the method of synthesis and the composition of the acetic acid (XVIII). The proportion of ^{13}C in the methyl group of this acetic acid was obtained by measurement of carbon dioxide

[31] J. D. Cox, H. S. Turner and R. J. Warne, *J. Chem. Soc.* 3167 (1950).
[32] J. C. Sauer, *J. Amer. Chem. Soc.* **69**, 2444 (1947).
[33] A. S. Spriggs, C. M. Hill and G. W. Senter, *J. Amer. Chem. Soc.* **74**, 1555 (1952).

from combustion of the acetic acid and of two specimens obtained from it by dilution with normal acetic acid. The mean value was 0·526 (52·6%).

In the 2:4-$^{13}C_2$-oxobutyl acetate (XXI) four species differing at positions 2 and 4 can be distinguished. The first (XXIV) has ^{13}C at both positions and constitutes $(0{\cdot}526)^2 = 0{\cdot}277$ of the whole; the proportion of the second (XXV), with ^{12}C at both positions, is $(1 - 0{\cdot}526)^2 = 0{\cdot}225$; the third and fourth (XXVI and XXVII), with ^{13}C at one position and ^{12}C at the other, each contribute $(0{\cdot}526 \times 0{\cdot}474) = 0{\cdot}249$. The calculation assumes random pairing of C_2 units in the formation of diketen. This assumption is not proved, but the normal extent of a ^{13}C-isotope effect is not sufficient to alter these proportions significantly in a reaction permitted, as this one was, to go to completion.

$^{13}CH_3CO^{13}CH_2CH_2OAc$ XXIV

$^{12}CH_3CO^{13}CH_2CH_2OAc$ XXV

$^{13}CH_3CO^{12}CH_2CH_2OAc$ XXVI

$^{12}CH_3CO^{13}CH_2CH_2OAc$ XXVII

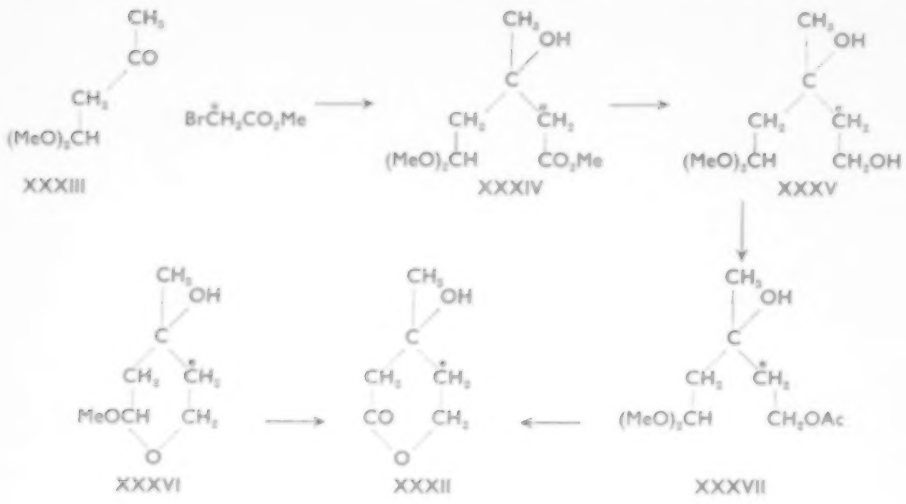
The isotopic composition of the 3′:4-$^{13}C_2$-mevalonolactone (XXIII) was also measured by combustion and mass spectrometry of the carbon dioxide: thus the precise degree of dilution at the 3-oxobutyl acetate stage was found. Although dilution was done before mevalonolactone was made, it will be convenient in what follows to speak of "undiluted mevalonolactone", meaning the fraction of lactone originating from the undiluted 2:4-$^{13}C_2$-oxobutyl acetate and therefore containing the four species (XXVIII–XXXI) in the same relative proportions as their progenitors (XXIV–XXVII). The lactone was further diluted with a small, known amount of 2-^{14}C-mevalonolactone before the biosynthesis; this facilitated measurement of yields.

XXVIII XXIX XXX XXXI

● = ^{13}C atom, ○ = ^{12}C atom.

An additional synthesis of mevalonolactone was devised to prepare 4-^{14}C labelled material (XXXII). 4:4-Dimethoxybutanone (XXXIII) with methyl 2-^{14}C-bromoacetate and zinc gave, as already reported by Eggerer and Lynen,[34] a hydroxy ester (XXXIV). This was reduced by lithium aluminium hydride; the resulting alcohol (XXXV) formed a pyranoside (XXXVI) rather easily on distillation and was preferably acetylated first. When the product (XXXVII) was heated with hydrogen peroxide in acetic acid containing a little sulphuric acid and the mixture after neutralisation of mineral acid was distilled, 4-^{14}C-mevalonolactone was obtained directly. The pyranoside (XXXVI) gave mevalonolactone in somewhat lower yield when treated in the same way.

[34] H. Eggerer and F. Lynen, *Liebigs Ann.* **608**, 71 (1957).

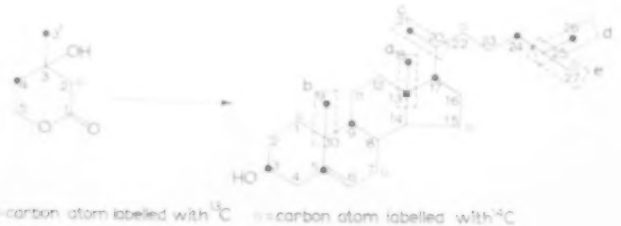


PREPARATION OF ^{13}C-CHOLESTEROL

To convert the 3′:4-$^{13}C_2$-mevalonolactone into cholesterol, a cell-free preparation of rat liver was made[35,21] by a modified technique which reduced the proportion of endogenous lipid. To increase further the proportion of newly biosynthesised material the amount of substrate taken was much larger than usual and the enzymes were kept active for as long as possible by repeated addition of co-factors. The cholesterol was separated, after saponification, as the digitonide, and recrystallised from methanol after recovery from the complex. Purification through the dibromide, which is wasteful of material, was not attempted, for the presence of other digitonin-precipitable steroids, even in large amount, could not affect the main calculations. Two specimens of cholesterol, having different degrees of dilution by endogenous material, were obtained.

DEGRADATION OF ^{13}C-CHOLESTEROL

Chromic oxidation of cholesterol can give acetic acid from four positions. The carboxyl groups of this acetic acid are supplied by $C_{(10)}$, $C_{(13)}$, $C_{(20)}$, and $C_{(25)}$, and the methyl groups by $C_{(19)}$, $C_{(18)}$, $C_{(21)}$, and $C_{(26)}$ *or* $C_{(27)}$ respectively (see Scheme 3). The positions in cholesterol and in mevalonolactone giving rise to the different types of acetic acid are correlated in Table 1. It can be seen that only one type of acetic acid, that from $C_{(18)} + C_{(13)}$ of cholesterol, has excess ^{13}C in its carboxyl groups.



• = carbon atom labelled with ^{13}C ○ = carbon atom labelled with ^{14}C

Scheme 3

[35] N. L. R. Bucher and K. McGarrahan, *J. Biol. Chem.* **222**, 1 (1956).

TABLE 1. ORIGIN OF CARBON ATOMS IN ACETIC ACID FROM OXIDATION OF CHOLESTEROL

Type of acetic acid (Scheme 3)	Position in cholesterol providing		Position in mevalonolactone providing	
	methyl	carboxyl	methyl	carboxyl
a	18	13	3′	4
b	19	10	3′	3
c	21	20	3′	3
d	26	25	3′	3
e	27	25	2	3

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Thus if the excess ^{13}C in the carboxyl groups of the total acetic acid is measured and divided by the excess ^{13}C at a labelled position in mevalonolactone (diluted or undiluted), the quotient is the proportion of acetic acid molecules originating from $C_{(3')}$–$C_{(4)}$ of the lactone. If the total ^{13}C content of the acetic acid is also known by combustion and measurement of the carbon dioxide, the ^{13}C content of the methyl groups, and thence the proportion of acetic acid molecules originating from $C_{(3')}$–$C_{(3)}$ of the lactone, can be calculated. This reasoning dictated the experimental procedure.

To minimize the possibility of rearrangements of methyl groups during oxidation, the ordinary Kuhn–Roth technique[36] using chromic and sulphuric acids was avoided. The isotopic cholesterol was stirred with boiling aqueous chromic acid until it dissolved; phosphoric acid and water were then added and the acetic acid was distilled by repeated evaporation. This is an adaptation of a method described[37] by Kuhn and L'Orsa. Between 2·8 and 3 molecules of acetic acid (70–75% of theory) were obtained from each molecule of cholesterol. The acid was isolated as silver acetate. Normal cholesterol was treated in the same way to provide the bases for determining excess of isotopic species.

Some of the silver acetate was treated with bromine in carbon tetrachloride and the carbon dioxide evolved was isolated as barium carbonate. This method of degradation was preferred since the only oxygen in the reaction mixture is present in the carboxylate groups and no carbon dioxide could possibly be formed from methyl groups.

Another part of the silver acetate was burned to provide carbon dioxide representing the total carbon. The remainder was used for mass spectrometry.

Cholesterol from 4-^{14}C-mevalonolactone was also oxidised and the silver acetate was treated as above to obtain barium carbonate representing (a) carboxyl groups and (b) total carbon. The radioactivity of (b) was, within experimental error, one-half that of (a). Specimens of cholesterol from 3′:4-$^{13}C_2$-mevalonolactone and from 4-^{14}C-mevalonolactone were also burned, and the carbon dioxide was assayed for ^{13}C and ^{14}C respectively. Hence the excess of isotope at each "labelled" position in the cholesterol could be calculated, assuming 10 labelled positions for cholesterol from the ^{13}C-lactone (cf. Scheme 3) and 6 for the ^{14}C-lactone. The proportion of the total

[36] R. Kuhn and H. Roth, *Ber. Dtsch. Chem. Ges.* **66**, 1274 (1933).
[37] R. Kuhn and F. L'Orsa, *Z. Angew. Chem.* **44**, 847 (1931).

acetic acid which contained labelled carboxyl groups could then be calculated and was found to be essentially the same (ca. 20%) for the ^{13}C and ^{14}C specimens. These measurements support the conclusions (i) that the methyl groups of the acetic acid from oxidation contain no carbon originating from $C_{(4)}$ of mevalonolactone, and (ii) that the excess ^{13}C in the carboxyl groups of the acetic acid originates entirely from $C_{(4)}$ of mevalonolactone.

MASS SPECTROMETRY OF ACETIC ACID

Published mass spectra of acetic acid[38] show a strong peak at mass 60 ($CH_3CO_2H^+$) and a minor peak at 61 (principally $^{13}CH_3CO_2H^+$ and $CH_3{}^{13}CO_2H^+$); we also found a still smaller peak at 62, attributable to $CH_3C^{18}OOH^+$ and minor proportions of other isotopic species. There were no background peaks at 60, 61 or 62, and no peaks in the acetic acid spectrum at 59 or 58; this simplified the analysis. Fragmentation of the acetic acid accompanies ionisation and is a possible source of error if the ^{13}C species are markedly less easily disintegrated than the ^{12}C species. We were able to measure this effect by comparing the values obtained for the mass 61 content of synthetic $^{13}CH_3CO_2H$ with the values deduced from measurement of carbon dioxide after combustion. The small difference between these two sets of values was taken as a measure of the isotope effect on fragmentation of acetic acid, and a corresponding correction was applied to the results obtained by direct measurement of the acetic acid from cholesterol. A further small correction must be made for the slightly altered distribution of ^{18}O, ^{17}O and D among the three peaks 60, 61 and 62.

Wood[39] reported unsuccessful attempts to measure directly the proportions of ^{13}C species in acetic acid, which he eventually converted into ethylene before measurement.

The difficulties were (i) preparation of pure acetic acid in small quantities, (ii) introduction into the spectrometer, and (iii) strong absorption on the instrument's walls. The first of these difficulties was overcome by preparing acetic acid in a closed system from dry silver acetate and dry hydrogen chloride, the second by arranging a pinhole leak fed by acetic acid vapour from a liquid sample held at constant temperature. Since the inlet system had a very small surface area, absorption on its walls was negligible. Absorption on the spectrometer walls still caused difficulty, for a new sample had to be run for some time before the contribution of the previous sample had been reduced to insignificance; but this could be accepted since relatively few samples were to be measured.

CONCLUSION

The calculation of the expected excess above normal of $^{13}C_1$- and $^{13}C_2$-acetic acids, in the acetic acid from oxidation of cholesterol, according to mechanisms (a) and (b), is detailed and explained in the experimental section. The calculated values for mechanism (a) are derived from three experimentally determined figures: the proportion of ^{13}C in the methyl group of the synthetic $^{13}CH_3CO_2H$, the excess ^{13}C in the carboxyl group of the acetic acid from oxidation of cholesterol, and the excess ^{13}C in the total carbon of the acetic acid from oxidation of cholesterol. For calculation by mechanism (b), the degree of dilution of the isotopic lactone before biosynthesis is also needed. Both calculations assume, as indicated above, random combination of

[38] G. P. Happ and D. W. Stewart, *J. Amer. Chem. Soc.* **74**, 4404 (1952).
[39] H. G. Wood, *J. Biol. Chem.* **194**, 905 (1952).

isotopic C_2 units during synthesis of mevalonolactone; there is also an implicit assumption that isotopic and normal molecules are used at random for biosynthesis of squalene. In addition, the calculation for mechanism (b) assumes that no further dilution of the mevalonolactone by endogenous intermediates occurs during biosynthesis of squalene; this assumption is not necessarily true. If such dilution does take place, the calculated value for $^{13}C_2$-acetic acid would be still lower and the value for $^{13}C_1$-acetic acid higher. The calculated values for mechanism (a) would be completely unaffected.

TABLE 2. OBSERVED AND CALCULATED EXCESS OF $^{13}C_1$- AND $^{13}C_2$-ACETIC ACID IN PRODUCT FROM OXIDATION OF CHOLESTEROL

Experiment	Quantity	Calc. for (a)	Observed	Calc. for (b)
I	% excess $^{13}C_1$-acetic	1·37	1·40	1·57
	% excess $^{13}C_2$-acetic	0·206	0·210	0·107
	Ratio $^{13}C_1/^{13}C_2$	6·65	6·67	14·7
II	% excess $^{13}C_1$-acetic	2·09	2·08	2·37
	% excess $^{13}C_2$-acetic	0·294	0·285	0·153
	Ratio $^{13}C_1/^{13}C_2$	7·11	7·30	15·5

The experimental and calculated results are set out in Table 2; the agreement between observed values and those calculated for mechanism (a) is excellent. The conclusion following unquestionably from the results is that during biosynthesis of cholesterol from mevalonolactone and subsequent chemical degradation to acetic acid, a carbon atom originating from position 3′ of the lactone migrates to a carbon atom originating from position 4 of the same molecule of lactone. This means that the migration, whenever it took place, was an intramolecular 1:2-shift.

If the rearrangement which undoubtedly occurs during enzymic cyclisation of squalene had taken place by mechanism (b), or intermolecularly, and was followed by further rearrangement during oxidation, it does not seem possible to explain the experimental figures by except assuming that a total migration of $C_{(19)}$ to $C_{(5)}$ during oxidation is accompanied by a total migration of $C_{(18)}$ to $C_{(14)}$ or $C_{(12)}$ (cf. Scheme 3). An oxidation of this sort could not be defended on chemical grounds. Rearrangement after biosynthesis therefore seems to be excluded.

A second possibility is that rearrangement during cyclisation of squalene to lanosterol takes place by mechanism (b) but is followed by intramolecular rearrangement during demethylation of lanosterol to cholesterol, the methyl group on $C_{(14)}$ migrating to $C_{(13)}$. But this methyl group would have to cross from the α-side to the β-side of the molecule during an intramolecular rearrangement, which seems most improbable. The same objection applies to an exchange of methyl groups in lanosterol itself.

A third possibility is that squalene cyclises by a mechanism of type (b) to give not lanosterol but a 13α:14β isomer, and that this rearranges, with exchange of methyl groups, to lanosterol. However, it is difficult to imagine a mechanism for this exchange; nor is there evidence to suggest that any intermediate substance intervenes between squalene and lanosterol.

Thus an intramolecular 1:2 shift according to mechanism (a) during cyclisation of squalene to lanosterol appears to be the only mechanism which needs no improbable assumptions to explain the results.

In an independent research simultaneous with ours, Maugdal, Tchen and Bloch[40] established, by studying the cyclisation of squalene labelled in a special manner with ^{13}C, that the methyl group attached to $C_{(14)}$ of lanosterol has also arrived there by migration. The results, though they do not exclude an intermolecular rearrangement, are entirely consistent with mechanism (a) and not with mechanism (b); and the two experimental approaches, dealing as they do with different methyl groups, are complementary. We are much indebted to Professor Bloch for communicating these results before publication.

EXPERIMENTAL

Preparation of isotopic mevalonolactones

Preparation of 2:4-$^{13}C_2$-3-*oxobutanol*. Sodium 2-^{13}C-acetate (6·584 g), prepared from $K^{13}CN$ by the method of Cox *et al.*,[31] was deposited evenly by freeze-drying on the walls of a flask and dehydrated at 220°/0·07 mm for 4 hr. Redistilled phthalyl chloride (55 ml) was added and the mixture was heated (bath 170°), the acetyl chloride distilling into a 3-necked flask cooled to −70° and equipped with an efficient stirrer and a dry-ice condenser. The last traces of acetyl chloride were driven over by brief heating with a free flame.

The acetyl chloride generator was disconnected and ether (80 ml) was distilled from lithium aluminium hydride into the 3-necked flask, which was then brought to room temperature. Dry, redistilled triethylamine (11·5 ml) was added during 1 hr to the vigorously stirred mixture; the temp. rose until the ether was refluxing. Finally the mixture was stirred for a further 2¼ hr, a tube fitted with a filter plug of glass wool was introduced, and the ethereal filtrate was pressed into another flask by means of dry nitrogen. The residue of triethylamine hydrochloride was washed twice with 50 ml portions of ether (dried by $LiAlH_4$).

The total filtrate was added in four portions to well-stirred ethereal lithium aluminium hydride (59 ml of 0·9 M) cooled at −70°. A yellow solid was formed immediately. The mixture was stirred for 2 hr and excess of hydride was decomposed by addition of ethereal ethyl acetate. Saturated aqueous $KHCO_3$ was then added until the solid coagulated. The mixture was filtered and the solid washed twice with ether. Distillation of the filtrate then gave 2:4-$^{13}C_2$-3-oxobutanol (0·711 g) as a colourless liquid, b.p. 76–78°/16 mm.

The identity of this product, though not its purity, had been previously established by submitting normal sodium acetate to identical procedures, when the product after redistillation gave an infra-red spectrum identical with that of 3-oxobutanol prepared from acetone and formaldehyde. When normal diketen was reduced as above, the maximum yield of 3-oxobutanol obtained was 48%. When normal acetyl chloride was condensed by triethylamine as above and the mixture treated with ethanolic sulphuric acid, ethyl acetoacetate was obtained in 70% yield.

2:4-$^{13}C_2$-3-*Oxobutyl acetate*. 2:4-$^{13}C_2$-3-oxobutanol (0·711 g) and dry ether (0·7 ml) were cooled to −15° and treated with a slight excess over one equivalent of keten. After 20 min the product was distilled to give 2:4-$^{13}C_2$-3-oxobutyl acetate (0·937 g)

[40] R. K. Maugdal, T. T. Tchen and K. Bloch, *J. Amer. Chem. Soc.* **80**, 2589 (1958).

b.p. 40°/0·1 mm. A product obtained similarly from normal 3-oxobutanol had an infra-red spectrum almost identical with that of 3-oxobutyl acetate prepared as described below: the spectrum in the carbonyl region indicated a small amount of impurity (diketen?).

3-*Hydroxy*-3-*methylpentano*-5-*lactone* (*mevalonolactone*). Normal 3-oxobutyl acetate was prepared by heating methyl vinyl ketone (35 g), acetic acid (150 ml) and water (1 drop) overnight under reflux. Fractionation gave recovered ketone and acid and 3-oxobutyl acetate (28·6 g; 44%), b.p. 78–84°/15 mm, which was freed from traces of acetic acid as described previously.[21] The infra-red spectrum was identical with that of an authentic specimen (made by acetylation of 3-oxobutanol with acetic anhydride). This process is an improvement on a patented procedure.[41]

3-Oxobutyl acetate (26 g) and dry ether (20 ml) were cooled (bath at −30°) and boron trifluoride etherate (0·6 ml) was added. Keten (slightly over 1 equiv.) was passed and the mixture was then left at −25° for 2 hr; some crystallisation usually occurred. The mixture was added, with the aid of more ether, to N methanolic potassium hydroxide (600 ml) cooled to −15°. The solution was kept overnight at room temperature, then neutralised (phenol red) by methanolic hydrogen chloride and evaporated at low pressure. The residue after washing with ether and chloroform was treated with methanol and then with sufficient methanolic hydrogen chloride to bring the total added to the equivalent of 592·4 ml of N (7·6 ml of N alkali is consumed by 0·6 ml boron trifluoride etherate). Potassium chloride was removed by filtration and the product, recovered by evaporation at low pressure, was extracted by chloroform. The filtered chloroform solution was distilled to give 24·9 g; b.p. 110°/0·01 mm. This contained a small amount of β-hydroxy*iso*valeric acid, since the keten was prepared as usual by pyrolysis of acetone and some acetone remained in the gas stream even though it had passed through a trap at −30° before entering the reaction vessel. The product was therefore treated with ethereal diazomethane until the yellow colour of the reagent persisted; redistillation then gave mevalonolactone (23·3 g; 90%), b.p. 114°/0·01 mm. (Found: C, 55·7; H, 7·7; Calc. for $C_6H_{10}O_3$: C, 55·4; H, 7·7%).

3′-4:$^{13}C_2$-3-*hydroxy*-3-*methylpentano*-5-*lactone*. 2:4-$^{13}C_2$-3-oxobutyl acetate (937 mg) was diluted with pure, normal 3-oxobutyl acetate (937 mg), and treated in ether with boron trifluoride and keten as described above. The product was isolated, also as described above; after second distillation the mevalonolactone (1·14 g) was dissolved in dry ether (20 ml) under reflux in a weighed conical flask. The solution was cooled, seeded and set aside at −5° for 24 hr. Large crystals separated and were isolated by decanting the mother liquor, washing rapidly with a little chilled ether and transferring the flask immediately to a vacuum desiccator. The crystalline hygroscopic 3′:4-$^{13}C_2$-mevalonolactone (813 mg) was the specimen used for biosynthesis and ^{13}C assay. A second crop was recovered from the mother liquor. A normal specimen, similarly prepared, had m.p. 28°.

Methyl 2-^{14}C-3-*hydroxy*-5:5-*dimethoxy*-3-*methylpentanoate*(XXXIV). Five portions of 2-^{14}C-bromoacetic acid (12·9 mg and 0·1 mC each) were esterified by ethereal diazomethane and normal methyl bromoacetate (1·223 g) was added. The whole was pipetted with the aid of ether (8 ml) into the reaction flask which contained activated zinc (1 g), ether (1·7 ml) and 4:4-dimethoxybutan-2-one (1·1 g). The

[41] du Pont, *U.S. Patent* 2,010,828 (1935).

mixture was stirred vigorously for 2½ hr. Reaction then set in suddenly; when it subsided the mixture was stirred and refluxed for 1½ hr and left for 18 hr.

A chilled mixture of acetic acid (0·5 ml) and water (3·5 ml) was added. The aqueous layer was saturated with ammonium chloride and extracted four times with ether which was then united with the ethereal layer, washed with a little saturated aqueous $KHCO_3$ (which was subsequently re-extracted with ether), dried ($MgSO_4$) and distilled. The acetal ester (1·09 g; 55%) had b.p. 60–70°/0·05 mm. Redistillation gave 0·986 g, b.p. 64–66°/0·05 mm.

4-Hydroxy-2-methoxy-4-methyltetrahydropyran (XXXVI). Lithium aluminium hydride (1·5 g) was stirred with tetrahydrofuran (30 ml) for 1 hr, cooled in ice water, and treated dropwise with normal methyl 3-hydroxy-5:5-dimethoxy-3-methylpentanoate (3 g) in tetrahydrofuran (20 ml). The mixture was stirred overnight at room temp., the hydride was decomposed by addition of ethyl acetate (9 ml), saturated aqueous ammonium chloride (9 ml) was added and the product was isolated in the usual manner. Distillation gave *4-hydroxy-2-methoxy-4-methyltetrahydropyran* (1·22 g; 1·1 g after redistillation), b.p. 60–62°/0·1 mm, as a colourless liquid. (Found: C, 57·4; H, 9·5; $C_7H_{14}O_3$ requires C, 57·5; H, 9·6%).

1-Acetoxy-2-^{14}*C-5:5-dimethoxy-3-methylpentan-3-ol* (XXXVII). Methyl 2-^{14}C-3-hydroxy-5:5-dimethoxy-3-methylpentanoate (0·968 g) in ether (5 ml) was stirred and cooled in ice during dropwise addition of 0·95 M ethereal lithium aluminium hydride (11 ml). After 30 min additional ether (2 ml) was added and the mixture was stirred at room temp. for 4 hr and refluxed for 1 hr. Ethereal ethyl acetate was added slowly until reaction ceased, then saturated aqueous $KHCO_3$ was added until the solid coagulated. The solid was washed on a filter with dry ether and the ethereal solutions were evaporated at low pressure. To the residue, pyridine (4 ml) and acetic anhydride (1 ml) were added. After 2½ hr the mixture was warmed for 20 min on a steam-bath and then distilled. The product (0·807 g, 80%) had b.p. 80–84°/0·003 mm. A non-isotopic specimen of the *1-acetoxy-5:5-dimethoxy-3-methylpentan-3-ol*, prepared similarly, was analysed (Found: C, 54·7; H, 8·9; $C_{10}H_{20}O_5$ requires C, 54·6; H, 9·1%).

4-^{14}*C-3-hydroxy-3-methylpentano-5-lactone* (*mevalonolactone*). 1-Acetoxy-2-^{14}C-5:5-dimethoxy-3-methylpentan-3-ol (0·807 g) was added to a mixture of acetic acid (2 ml), 30% hydrogen peroxide (1 ml), water (2 ml) and sulphuric acid (0·02 ml; d 1·84). The mixture was refluxed for 1 hr, anhydrous potassium carbonate (100 mg) was added and the solution was evaporated at low pressure. The residue was extracted with chloroform; distillation of the extract gave 4-^{14}C-mevalonolactone (322 mg; 68%), which was crystallised from ether (6 ml) as described earlier to give a first crop (0·143 g) used for biosynthesis. A non-isotopic specimen was prepared in the same way in 77% yield.

Mevalonolactone was also obtained in 59% yield by oxidising the pyranoside (XXXVI) in the same way.

Biosynthesis of cholesterol from isotopic mevalonolactones

Experiment with 2-^{14}*C-mevalonolactone*. This preliminary run was made to determine the advantage gained by adding co-factors at intervals during incubation and to try whether free cholesterol formed during incubation would be less diluted by endogenous material than total (free and esterified) cholesterol.

Rat liver (25 g; from 6 rats) was homogenised by the method of Bucher and McGarrahan[20] in 0·1 M phosphate buffer (62·5 ml; pH 7·4–7·5) containing nicotinamide (0·03 M) and magnesium chloride (0·004 M). The homogenate was centrifuged at 700 g for 25 min at 0° and decanted through several layers of gauze to remove a fatty layer. The supernatant was centrifuged at 10,000 g for 25 min at 0°, and again decanted through gauze from the residue of mitochondria. The supernatant fraction containing microsomes and soluble enzymes[21] is referred to as S_{10}.

Three flasks each containing S_{10} (10 ml) and 2-^{14}C-mevalonolactone (21 μmoles; 0·04 μC/μmole) were incubated aerobically at 37°. After 1 hr, DPNH (5 μmoles), TPN (2·5 μmoles), ATP 25 (μmoles) and ascorbate (75 μmoles) were added to flasks 2 and 3. After 2 hr, the same additions were made to flask 3 alone. After 3 hr, each flask was emptied into alcohol–ether (3:1 v/v; 100 ml + 50 ml for rinsing). The solutions were boiled for 1 min, filtered (Whatman No. 43 paper) and evaporated at low pressure (bath 40–50°). The residue was extracted with light petroleum (b.p. 40–60°); the extract after being clarified by centrifugation was brought to a volume of 1·3 ml in another centrifuge tube. Acetone (5 vol) and magnesium chloride (2 drops of saturated solution in ethanol) were added and after 1 hr at 0° the precipitate of phospholipids was centrifuged. The supernatant and two washings (acetone) were evaporated to 1 ml in another centrifuge tube and digitonin (5 ml of 0·5% in 90% ethanol) and N hydrochloric acid (6 drops) were added. The precipitate was centrifuged, washed with 1:1 alcohol-ether, 1:1 acetone-ether, and acetone (2 ml of each), suspended in acetone and collected on a weighed disk, area 2 cm², of Whatman No. 54 paper for counting.[42] The results are shown in Table 3.

TABLE 3. INCORPORATION OF 2-^{14}C-MEVALONOLACTONE INTO FREE AND ESTERIFIED CHOLESTEROL

Flask	Digitonides (mg)	Corrected counts/min at inf. thickness	Total ^{14}C in sterol, μC × 10^{-2}	Mevalonolactone incorporated, μM
1 (no cofactors added)	6·7 (free)	17,300	92·6	2·64
	1·3 (esters)	10,911	11·3	0·34
2 (cofactors added after 1 hr)	6·9 (free)	29,400	162	4·88
	1·4 (esters)	28,300	31·7	0·96
3 (cofactors added after 1 and 2 hr)	7·4 (free)	32,530	193	5·78
	1·7 (esters)	34,400	46·8	1·4

The supernatant and washings from the digitonide were reduced to 1·5 ml and ether (5 vol) was added to precipitate digitonin. The supernatant was then evaporated and the residue dissolved in light petroleum (b.p. 40–60°). This was clarified by centrifuging, reduced to 0·5 ml and treated with ethanol (1 ml) and 4 N KOH (0·5 ml).

[42] G. Popják, *Biochem. J.* **46**, 560 (1950).

The mixture was heated (bath 80°) for 1½ hr then extracted with light petroleum. The extracted material in acetone (0·5 ml) was treated with digitonin solution (2 ml) and N HCl (6 drops). The digitonides were prepared for counting as before (Table 3).

Thus a total of 7·2 μmoles of mevalonolactone had been incorporated into cholesterol in flask 3 which had received two additions of cofactors. Since the theoretical maximum from 21 μmoles of DL-lactone is probably 10·5 μmoles, this procedure was considered satisfactory and was used in the ^{13}C experiments.

Experiments with 2-^{14}C-3′:4-$^{13}C_2$-*mevalonolactone*. S_{10} was prepared from ca. 130 g of liver pulp from 25 white rats. The 3′:4-$^{13}C_2$-mevalonolactone (524 mg) described above was mixed with 2-^{14}C-mevalonolactone (18 mg; 0·2 μC/μmole).

Ten flasks each containing S_{10} (20 ml) and the labelled lactone (40 μmoles) were incubated aerobically at 37°. After 1 hr and 2 hr, each flask received DPNH (10 μmoles), TPN (5 μmoles), ATP (50 μmoles) and ascorbate (150 μmoles). After 3½ hr, potassium hydroxide (2 g pellets) and ethanol (20 ml) were added to each flask. After being heated overnight on a steam-bath the contents of the flasks were pooled and extracted thrice with light petroleum (b.p. 40–60°) which was then washed with water, dried ($MgSO_4$) and evaporated at low pressure (bath 50°). An aliquot (0·5 ml) of a solution (10 ml) of the residue in acetone was taken and a digitonide prepared from this as described above.

Five such experiments were run; the weights and radioactivities of the digitonides are given in Table 4.

Table 4. Yields and radioactivities of digitonides from 2-^{14}C-3′:4-$^{13}C_2$-mevalonolactone

Experiment	Digitonide (mg)	Counts/min at inf. thickness
1	9·5	2840
2	13·5	3290
3	17·9	2347
4	12·3	4560
5	14·1	4400

In the first three experiments the liver homogenate was spun at 700 g for 10 min, instead of 25 min. Although the reason for the superiority of a 25 min period was not rigorously established we believe that more endogenous sterol (as a lipoprotein complex?) is carried down when spinning is prolonged.

From the combined product of Experiments 1, 2 and 3, 680 mg of digitonide were isolated. This was dissolved in acetic acid (60 ml), boiled for 5 min, cooled and treated with ether (300 ml). The precipitate was centrifuged and washed twice with ether. The ethereal solution after washing with water (4 × 200 ml), and with M sodium hydrogen carbonate until neutral, was dried ($MgSO_4$) and evaporated to leave crude cholesterol (139 mg). Recrystallisation from methanol gave colourless plates (114·5 mg), m.p. 143–144°. This was the "more dilute" cholesterol used in Exp. I.

From the combined products of experiments 4 and 5 digitonide (504 mg), crude sterol (115 mg), and recrystallised sterol (75 mg; m.p. 142–143°) were obtained in

the same way. The recrystallised material ("less dilute" cholesterol) was used in Exp. II.

Cholesterol was prepared from 4-^{14}C-mevalonolactone in the same way. A portion (10·5 mg) of the product was mixed with purified cholesterol (76·9 mg) and the whole recrystallised from methanol to give 69 mg.

Degradation of cholesterol to silver acetate

Experiment I. The "more dilute" cholesterol (96·5 mg) was melted on the walls of a 50 ml flask fitted with a side tubulature. A solution of chromium trioxide (5 g) in water (12·5 ml) was added, a platinum Hershberg-type stirrer operating through a reflux condenser was fitted and the mixture was boiled gently with stirring for 11 hr, when very little insoluble material remained. The condenser and stirrer were removed and rinsed with a little water, a spray-trap and condenser were fitted, phosphoric acid (3 ml; d 1·75) was added and the mixture was distilled until the residue began to foam. Successive quantities of water (ca. 10 ml) and fresh porous pot were added through the tubulature after each distillation. After six distillations the total distillate was heated to boiling and neutralised to phenol red with 0·1 N NaOH (7·40 ml). The liquid was concentrated at low pressure to ca. 2 ml, treated with aqueous silver nitrate (2·5 ml of 5%), filtered hot from traces of silver chromate, concentrated and treated with a little ethanol. Silver acetate crystallised and was collected. Two crops (85 + 20 mg) were obtained (Found: Ag, 64·5; Calc. for $C_2H_3O_2Ag$: 64·65%).

Experiment II. The "less dilute" cholesterol (72 mg) was oxidised as above to give silver acetate (77 mg) (Found: Ag, 64·8%). Cholesterol (50·4 mg) from 4-^{14}C-mevalonolactone was oxidised as above to give silver acetate (49 mg).

A normal specimen of cholesterol was also oxidised to acetic acid as above.

Preparation of Samples for Measurement of Isotopes

Mass spectrometry of acetic acid

Combustions. Weighed samples were burned in oxygen in a micro-combustion furnace (quartz tube filled with copper oxide, 700°). The issuing gases passed through two bubblers each charged with half-saturated barium hydroxide solution (4 ml) and light petroleum (b.p. 100–120°; 4 ml). A significant amount of barium carbonate was never found in the second bubbler, provided that the bubbles produced in the first bubbler were small. Each bubbler had a detachable head consisting of a B24 socket carrying inlet and outlet tubes; the lower part was a heavy-walled tube surmounted by a B24 cone. After the combustion the heads were removed and rinsed with CO_2-free water. The tubes were then centrifuged and the aqueous layer withdrawn. The barium carbonate was stirred and centrifuged three times with CO_2-free water, then twice with CO_2-free ethanol, and finally dried at 100°.

The following samples were burned in this way:

(i) Silver acetate from synthetic $^{13}CH_3CO_2Na$ (Found: Ag 64·3; Calc. for $C_2H_3O_2Ag$ with 0·52 atom excess ^{13}C per molecule: 64·4%).

(ii) Silver acetate prepared by recrystallising a mixture of (i) (5·85 mg) and normal silver acetate (82·2 mg). This is a dilution of 1 in 15·1 (Found: Ag 64·5%).

(iii) Silver acetate prepared by recrystallising a mixture of (i) (3·61 mg) and normal silver acetate (86·63 mg). This is a dilution of 1 in 25 (Found: Ag 64·7%).

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(iv) Silver acetate from oxidation of cholesterol from 4-^{14}C-mevalonolactone (Found: Ag 64·3%).

(v) Silver acetate from oxidation of cholesterol from 2-^{14}C-3′:4-$^{13}C_2$-mevalonolactone (Exp. I).

(vi) As (v) (Exp. II).

(vii) Cholesterol from 4-^{14}C-mevalonolactone.

(viii) Cholesterol from 2-^{14}C-3′:4-$^{13}C_2$-mevalonolactone (Exp. I).

(ix) As (viii) (Exp. II).

(x) 3′:4-$^{13}C_2$-mevalonolactone (as synthesised).

(xi) Normal cholesterol.

Degradation of silver acetate. A small flask fitted with a bubbler tube, side-tube, dry-ice condenser and magnetic stirrer was charged with silver acetate (ca. 20 mg), swept out with dry, CO_2-free nitrogen, and connected to two baryta bubblers prepared as above. The gas stream was regulated, the condenser was cooled to −70° and bromine (0·03 ml) in carbon tetrachloride (1 ml), both dried over phosphoric oxide, was introduced quickly through the side-tube. The mixture was then stirred and heated at 40–50° for 2 hr. The barium carbonate was collected as described above: in general its weight was slightly less than that of the silver acetate (70–80% yields).

The specimens degraded in this way were:

(i) Silver acetate from cholesterol from 4-^{14}C-mevalonolactone.

(ii) Silver acetate from ^{13}C-^{14}C-cholesterol (Exp. I).

(iii) As (ii) (Exp. II).

Assay of ^{14}C in barium carbonate specimens. The specimens were counted as "infinitely thick" layers on 1 cm² polythene disks by means of a thin-mica-window Geiger–Müller counter, and counting was continued sufficiently long to reduce the standard error of the counts below 2%.

Assay of ^{13}C in barium carbonate specimens. The specimens were decomposed in Rittenberg tubes by CO_2-free 4% hydrochloric acid and the carbon dioxide was measured in the normal manner.

Preparation of acetic acid for mass spectrometry. The apparatus is shown in Fig. 1, A and B. Silver acetate (44–45 mg) was introduced into the flask A which was then evacuated and dried. The tube B, which contained a little phosphorus pentoxide, was filled with dry hydrogen chloride at atmospheric pressure by means of a glass probe inserted through the stopcock to the bottom of the tube. Tube B then contained slightly less than 1 equivalent of hydrogen chloride. The hydrogen chloride was transferred by vacuum-line technique, using liquid air, to the flask A, which was sealed and detached at the constriction. The flask was then heated in boiling water, when acetic acid distilled into the capillary side-tube. Heating was continued for 2 hr, the acetic acid being occasionally driven back into the flask. Finally the capillary tube was sealed. The melting-point of the acetic acid was then determined.

Six specimens were so prepared:

(i) Acetic acid from oxidation of "more dilute" cholesterol (Exp. I); m.p. 15·5–16°.

(ii) Acetic acid from oxidation of "less dilute" cholesterol (Exp. II); m.p. 14·5–15·5°.

(iii) Acetic acid from normal cholesterol; m.p. 15·5–16°.

(iv) Synthetic ^{13}C acetic acid (undiluted).

(v) (iv), diluted 1 : 14·1 with normal material.
(vi), (iv), diluted 1 : 24 with normal material.

Mass spectrometry of acetic acid. The spectrometer used was a 60° instrument with Nier type ion source. Ionising potential was 70 V and accelerating potential 1620 V for mass 60. The special inlet is shown in Fig. 1, C. A capillary tube containing acetic acid, prepared as above, was opened at both ends and the liquid was

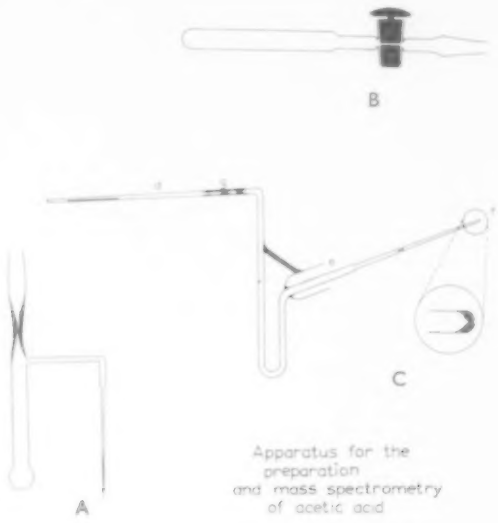

FIG. 1.

touched with a finer capillary until a little acetic acid (1–2 mg) had been transferred. The reservoir of acetic acid was resealed. The smaller capillary was sealed at one end and introduced into the thin horizontal tube d, which was connected to the spectrometer at e. The thin tube was sealed and a cooling bath was placed around the U-tube. As air was removed into the spectrometer through the pinhole leak at f, which projected as far as possible into the spectrometer, acetic acid distilled into the U-tube. When evacuation was complete (2–3 hr), the cooling bath was replaced by a Dewar flask containing water at a temperature which allowed acetic acid vapour to enter the spectrometer at a convenient rate (in this apparatus, ca. 10°). Measurements were then made at masses 60, 61 and 62 and were continued at intervals during that day and the next day. When the previous sample was not too different in composition, values became constant after several hours; but only the second day's readings were used. After a determination, the whole inlet was warmed in hot air to expel adsorbed acetic acid. The horizontal tube was then opened, the constrictions at g preventing dust and fragments of glass from reaching the pinhole.

The first inlet designed used a sintered glass valve sealed by mercury.[43] This was found unsatisfactory because of the tendency of acetic acid to accumulate (perhaps partly as metallic acetates) in the sintered glass.

The six acetic acid specimens prepared as above were measured.

[43] R. C. Taylor and W. S. Young, *Industr. Engng. Chem.* (*Anal.*) **17**, 811 (1945).

CALCULATIONS

The normal isotopic abundances assumed in the following calculations are: ^{13}C, 1·11%; ^{18}O, 0·20%; ^{17}O, 0·037%; D, 0·016%.

(1) ^{12}C *Content of* CO_2 *from mass-spectrometric readings*

If x is the proportion of ^{13}C in the sample, and $(1 - x)$ the proportion of ^{12}C, the strength of signal at 44 relative to that at 45 (ratio R) differs slightly from $(1 - x)/x$ for several reasons: overlap of peaks, differential pumping of isotopes, differential speed through pinhole, differential cracking on ionisation, and finally the presence of ^{17}O in the sample, which increases peak 45 at the expense of 44. Since the R value found for carbon dioxide from "normal" cholesterol (see Table 6) does not differ

Table 5. Measurements of radioactivity of $BaCO_3$ specimens

No.	Origin of sample	Method of prepn.	Corrected counts/min
(i)	^{13}C-^{14}C-cholesterol (Exp. I)	Combustion	377
(ii)	^{13}C-^{14}C-cholesterol (Exp. II)	Combustion	533·5
(iii)	Silver acetate from oxidn. of (i)	Combustion	165
(iv)	Silver acetate from oxidn. of (ii)	Combustion	257
(v)	Cholesterol from 4-^{14}C-mevalonolactone	Combustion	264
(vi)	Silver acetate from oxidn. of (v)	Combustion	128
(vii)	Silver acetate from oxidn. of (v)	Br_2–CCl_4	249

Table 6. Measurement of ^{13}C content of $BaCO_3$ specimens

No.	Origin of sample	Method of prepn.	Ratio 44/45 (R)	Uncorrected ^{13}C content (x)	Corrected ^{13}C content	Atom % excess ^{13}C
(i)	Normal cholesterol	Combustion	80·6	0·01225	0·0111	—
(ii)	$^{13}CH_3CO_2Ag$ (undiluted)	Combustion	2·70	0·2703	0·2692	25·81
(iii)	$^{13}CH_3CO_2Ag$ (diluted 1 : 14·1)	Combustion	33·3	0·02915	0·02800	1·690
(iv)	$^{13}CH_3CO_2Ag$ (diluted 1 : 24)	Combustion	43·2	0·02262	0·02147	1·037
(v)	3′;4-$^{13}C_2$-Mevalonolactone	Combustion	9·53	0·09497	0·09382	8·272
(vi)	^{13}C-cholesterol (Exp. I)	Combustion	52·9	0·01855	0·01740	0·630
(vii)	^{13}C-cholesterol (Exp. II)	Combustion	45·6	0·02146	0·02031	0·921
(viii)	CH_3CO_2Ag from oxidn. (Exp. I)	Combustion	46·3	0·02114	0·01999	0·889
(ix)	CH_3CO_2Ag from oxidn. (Exp. II)	Combustion	38·0	0·02564	0·02449	1·339
*(x)	As (viii)	Br_2–CCl_4	62·0	0·01587	0·01472	0·362
*(xi)	As (ix)	Br_2–CCl_4	56·5	0·01739	0·01624	0·514

* A duplicate determination gave an identical result.

materially from that found for other "normal" specimens of carbon dioxide in this spectrometer, we set the ^{13}C content of this carbon dioxide at 1·11% instead of the value 1·225% found by applying the formula $R = (1 - x)/x$. The correction, 0·115‰, assumed to represent the sources of error mentioned above, is applied to the other values of x calculated from the same formula. Thence the ^{13}C contents and atom % excess ^{13}C of the last two columns in Table 6 are derived.

(2) ^{13}C *Content of the methyl group in synthetic* $^{13}CH_3CO_2H$

(a) *By combustion.* In specimens (ii), (iii) and (iv) of Table 6, the labelled methyl group is associated with a normal carboxyl group, so that atom % excess in the methyl group is twice that of the CO_2 from combustion. Atom % excess ^{13}C in methyl group:

From (ii): $2 \times 25{\cdot}8 = 51{\cdot}6\%$; $\therefore$ ^{13}C content $= 0{\cdot}516 + 0{\cdot}011 = 0{\cdot}527$

From (iii): $2 \times 1{\cdot}69 \times 15{\cdot}1 = 51{\cdot}1\%$; $\therefore$ ^{13}C content $= 0{\cdot}511 + 0{\cdot}011 = 0{\cdot}522$

From (iv): $2 \times 1{\cdot}037 \times 25 = 51{\cdot}9\%$; $\therefore$ ^{13}C content $= 0{\cdot}519 + 0{\cdot}011 = 0{\cdot}530$

(b) *By direct measurement.* The data in Table 7, nos. (i), (ii) and (iii), were

TABLE 7. MEASUREMENT OF ACETIC ACID SPECIMENS IN THE MASS SPECTROMETER

(Results are expressed as percentages of the sum of the three peaks [in No. (i), two peaks] measured)

No.	Sample	Mass 60	Mass 61	Mass 62
(i)	$^{13}CH_3CO_2H$ (undiluted)	45·9	54·1	Not included
(ii)	$^{13}CH_3CO_2H$ (diluted 1 : 14·1)	93·66	5·85	0·486
(iii)	$^{13}CH_3CO_2H$ (diluted 1 : 24)	94·96	4·55	0·487
(iv)	CH_3CO_2H from Exp. I	95·43	3·91	0·665
(v)	CH_3CO_2H from Exp. II	94·66	4·60	0·742
(vi)	CH_3CO_2H from normal cholesterol	97·06	2·49	0·451

obtained by direct measurement. To derive the ^{13}C content of the methyl group from (ii) and (iii), the following procedure is used. The % excess of mass 61 above normal in (ii) is 3·36 and in (iii) is 2·06. By a calculation similar to that given later [Section (8)] the effects of redistribution of ^{18}O, ^{17}O and D are determined; thus, the % excess of $^{13}C_1$-acetic acid in (ii) is found to be $3{\cdot}36 + 0{\cdot}02 = 3{\cdot}38$, and in (iii) $2{\cdot}06 + 0{\cdot}015 = 2{\cdot}075$. Then from (ii), the undiluted acetic acid has

$$3{\cdot}38 \times 15{\cdot}1 = 51{\cdot}0\%,$$

and from (iii), $2{\cdot}075 \times 25 = 51{\cdot}9\%$ $^{13}C_1$-acetic acid above normal.

Now if x be the proportion of ^{13}C in the methyl group of the undiluted acetic acid, then the proportion of $^{13}CH_3{}^{12}CO_2H$ molecules is

$$x(1 - 0{\cdot}0111),$$

and of $^{12}CH_3{}^{13}CO_2H$ molecules,

$$0{\cdot}0111(1 - x).$$

The normal abundance of each of these species is

$$0{\cdot}0111(1 - 0{\cdot}0111)$$

Thus % excess of $^{13}C_1$-acetic acid is

$$x(1 - 0{\cdot}0111) + 0{\cdot}0111(1 - x) - 2 \times 0{\cdot}0111(1 - 0{\cdot}0111) \times 100 = 97{\cdot}78x - 1{\cdot}09$$

When $97{\cdot}78x - 1{\cdot}09 = 51{\cdot}0$

$$x = 0{\cdot}533.$$

When $97{\cdot}78x - 1{\cdot}09 = 51{\cdot}9$

$$x = 0{\cdot}542.$$

For calculations from (i), "% excess mass 61 above normal" is not a reliable basis since peaks 60 and 61 are of comparable size and the effect of overlap is largely neutralised.

The experimental ratio of the heights of the 61 and 60 peaks in (i) is 1·18. Isotopes besides ^{13}C affecting this ratio are ^{17}O and D, since introduction of one of either of these atoms converts a molecule of mass 60 to mass 61.

Let x be the ^{13}C content of the methyl group. Then a proportion x of the acetic acid molecules have a ^{13}C-methyl group and of these $(0{\cdot}0111 + 2 \times 0{\cdot}00037 + 4 \times 0{\cdot}00016)x = 0{\cdot}01248x$ have also a ^{13}C-carboxyl group, a ^{17}O or a D atom and therefore do not contribute to the 61 peak. The remaining proportion $(1 - x)$ forms the 60 peak except for 0·01248 $(1 - x)$ which is added to the 61 peak.

$$\text{Thus } \frac{x + 0{\cdot}01248(1 - x) - 0{\cdot}01248x}{0{\cdot}98752(1 - x)} = 1{\cdot}18$$

whence $x = 0{\cdot}539$.

The six values obtained for the ^{13}C content of the methyl group are therefore 0·522, 0·527, 0·530 (from CO_2 measurements), 0·533, 0·539, 0·542 (from acetic acid measurements).

As indicated earlier, the second measurements are probably higher because of an isotope effect in the extensive fragmentation of acetic acid molecules occurring during ionisation, a ^{12}C–^{13}C bond being slightly less easily broken than a ^{12}C–^{12}C bond. Since this effect is not large, we have previously[44] taken the mean of all six figures as the basis for further calculations. Another method is to use the difference between the two set of figures as a measure of the ^{13}C isotope effect in the mass spectrometry of acetic acid, and this method will be used here. Thus the mean value from the carbon dioxide measurements is 0·526, and the mean value from the acetic acid measurements is 0·538. We therefore assume that in mass spectrometry of acetic acid, $^{13}C_1$-acetic acid is over-represented to the extent of 2%; it follows that $^{13}C_2$-acetic acid is over-represented to the extent of 4%. These corrections will be applied to the results of mass spectrometry of the acetic acid from oxidation of cholesterol.

The proportion of ^{13}C in the methyl group of the synthetic acetic acid is therefore taken as 0·526; the atom % excess ^{13}C is $52{\cdot}6 - 1{\cdot}1 = 51{\cdot}5$.

(3) *Degree of dilution of* 3-*oxobutyl acetate before synthesis of* 3′:4-$^{13}C_2$-*mevalonolactone*

Since the 3′:4-$^{13}C_2$-mevalonolactone has 8·272% excess ^{13}C [Table 6; (v)] and 2/6 of its carbon atoms are labelled, a labelled position has $8{\cdot}272 \times 3 = 24{\cdot}816$

[44] J. W. Cornforth, R. H. Cornforth, A. Pelter, M. G. Horning and G. Popják, *Proc. Chem. Soc.* 112 (1958).

atom % excess ^{13}C. Since the acetic acid from which the 3-oxobutyl acetate was made contained 51·5 atom % excess ^{13}C in its methyl group, this is also the degree of labelling at positions 2 and 4 of the oxobutyl acetate, which was therefore diluted with [(51·5/24·816) − 1] = 1·075 parts of normal material before conversion into mevalonolactone.

The further dilution of mevalonolactone with 2-^{14}C-mevalonolactone before biosynthesis (18 mg, normal in ^{13}C, added to 524 mg) gives the mevalonolactone used in biosynthesis the following composition:

1 part "undiluted mevalonolactone" (i.e. derived from undiluted 3-oxobutyl acetate)

1·15 parts "normal mevalonolactone".

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(4) *Proportion of endogenous material in cholesterol biosynthesised from* 2-^{14}C-3′:4-$^{13}C_2$-*mevalonolactone*

The mevalonolactone used in biosynthesis had (allowing for dilution by radioactive material) 24·0 atom % excess ^{13}C at its labelled positions. The cholesterol is presumed (see Scheme 3) to have 10 labelled positions out of 27. Now the total carbon of cholesterol used in Exp. I had 0·630 atom % excess ^{13}C, and in Exp. II 0·921 % (Table 6; (vi) and (vii)); hence the dilution factors are

$$\text{Exp. I:} \qquad 24{\cdot}0 \Big/ \left(0{\cdot}630 \times \frac{27}{10}\right) = 14{\cdot}1$$

$$\text{Exp. II:} \qquad 24{\cdot}0 \Big/ \left(0{\cdot}921 \times \frac{27}{10}\right) = 9{\cdot}65$$

(5) *Proportions of labelled molecules in "undiluted mevalonolactone"*

Since the isotopic acetic acid contained 52·6 atom % ^{13}C in its methyl group, the "undiluted mevalonolactone" contains the following proportions of molecules differing at $C_{(2')}$ and $C_{(4')}$:

(i) ^{13}C at $C_{(2')}$ and $C_{(4)}$: 0·526 × 0·526 × 100 = 27·67 %
(ii) ^{13}C at $C_{(2')}$, ^{12}C at $C_{(4)}$: 0·526 × 0·474 × 100 = 24·93 %
(iii) ^{12}C at $C_{(2')}$, ^{13}C at $C_{(4)}$: 0·474 × 0·526 × 100 = 24·93 %
(iv) ^{12}C at $C_{(2')}$ and $C_{(4)}$: 0·474 × 0·474 × 100 = 22·47 %

(6) *Relative proportions of molecules, in the acetic acid from oxidation of cholesterol, originating from* $C_{(3')}$–$C_{(4)}$ *and from* $C_{(3')}$–$C_{(3)}$ *of mevalonolactone*

All excess ^{13}C in the *carboxyl* group of this acetic acid is provided by molecules originating from $C_{(18)}$–$C_{(13)}$ of cholesterol, *i.e.*, from $C_{(3')}$–$C_{(4)}$ of mevalonolactone (see Scheme 3). The excess ^{13}C in the *methyl* group is partly provided from the same source and partly from other molecules having a labelled methyl group ($C_{(3')}$ of mevalonolactone) attached to a normal carboxyl group ($C_{(3)}$ of mevalonolactone). These other molecules originate from $C_{(14)}$–$C_{(10)}$, $C_{(21)}$–$C_{(20)}$, and $C_{(26\text{ or }27)}$–$C_{(25)}$ of cholesterol.

Exp. I. The carboxyl group of the acetic acid contained 0·362 atom % excess

^{13}C, and the total carbon (methyl + carboxyl) contained 0·889 atom % excess. [Table 6; (viii) and (x)]. Then if x is the % excess ^{13}C in the methyl group,

$$\frac{0{\cdot}362 + x}{2} = 0{\cdot}889,$$

$$\text{whence } x = 1{\cdot}416$$

Now since $C_{(18)}$ of cholesterol contributes 0·362% excess ^{13}C to the carboxyl group of the acetic acid, $C_{(18)}$, which is attached to it and is also a labelled position, contributes 0·362% excess ^{13}C to the methyl group. The remaining 1·416 − 0·362 = 1·054% is supplied by acetic acid originating from other positions, i.e., from $C_{(3')}$–$C_{(3)}$ of mevalonolactone. Hence 1·054/0·362 = 2·912 times as many molecules of acetic acid originate from $C_{(3')}$–$C_{(3)}$ of mevalonolactone as from $C_{(3')}$–$C_{(4)}$.

Exp. II. Here

$$\frac{0{\cdot}514 + x}{2} = 1{\cdot}339$$

$$x = 2{\cdot}164,$$

and the ratio sought is

$$\frac{2{\cdot}164 - 0{\cdot}514}{0{\cdot}514} = 3{\cdot}210$$

(7) *Calculation of % excess $^{13}C_2$-acetic acid and $^{13}C_1$-acetic acid, expected in the acetic acid from oxidation of cholesterol, according to mechanisms* (a) *and* (b)

This acetic acid contained 0·362 atom % excess ^{13}C (Exp. I) and 0·514 atom % excess ^{13}C (Exp. II) in its carboxyl group. Since the undiluted mevalonolactone contained 51·5 atom % excess ^{13}C at a labelled position it follows that a fraction 0·362/51·5 (Exp. I) or 0·514/51·5 (Exp. II) of the total acetic acid had a carboxyl group derived from $C_{(4)}$ of this undiluted lactone. That is, out of each 1,422,700 (Exp. I) or 1,001,900 (Exp. II) molecules of the total acetic acid, 10,000 originate from $C_{(3')}$–$C_{(4)}$ of the undiluted lactone. Out of these totals another 10,000 × 2·912 = 29,120 (Exp. I), or 10,000 × 3·210 = 32,100 (Exp. II) molecules originate from $C_{(3')}$–$C_{(3)}$ of the undiluted lactone.

Mechanism (a). By this mechanism, each of the 10,000 molecules of acetic acid originating from $C_{(3')}$–$C_{(4)}$ of undiluted lactone has methyl and carboxyl groups originating from the same molecule of lactone, and the proportions given in Section (5) apply: that is, 2767 of the 10,000 are $^{13}CH_3{}^{13}CO_2H$, 2493 are $^{13}CH_3{}^{12}CO_2H$ and 2493 are $^{12}CH_3{}^{13}CO_2H$. The acetic acid originating from $C_{(3')}$–$C_{(3)}$ of the undiluted mevalonolactone contains a labelled carbon (52·6 atom % ^{13}C) and a normal carbon (1·11 atom % ^{13}C); it therefore contains a proportion (0·526 × 0·0111) of $^{13}C_2$-acetic acid and [0·526(1 − 0·0111) + 0·0111(1 − 0·526)] of $^{13}C_1$-acetic acid. That is, of the 29,120 molecules in Exp. I, 170 are $^{13}C_2$-acetic acid and 15,300 are $^{13}C_1$-acetic acid; of the 32,100 molecules in Exp. II, 187 are $^{13}C_2$-acetic and 16,865 are $^{13}C_1$-acetic acid.

Then in Exp. I, a total of 39,120 molecules contains 2937 molecules of $^{13}C_2$-acetic acid and 20,286 molecules of $^{13}C_1$-acetic, against a normal abundance of 5 and 859 molecules respectively. In Exp. II, a total of 42,100 molecules contains 2954

molecules of $^{13}C_2$-acetic acid and 21,851 of $^{13}C_1$-acetic acid, against a normal abundance of 5 and 924 respectively. The rest of the acetic acid in each specimen is normal with respect to ^{13}C. Thus in the total acetic acid of Exp. I, 1,422,700 molecules contain 2932 molecules of $^{13}C_2$-acetic acid and 19,427 molecules of $^{13}C_1$ acetic acid above normal; in Exp. II, 1,001,900 molecules contain 2949 molecules of $^{13}C_2$-acetic and 20,927 molecules of $^{13}C_1$-acetic acid above normal. Thus the expected proportions by mechanism (a) are:

	% excess $^{13}C_1$-acetic acid	% excess $^{13}C_2$-acetic acid
Exp. I	1·37	0·206
Exp. II	2·09	0·294

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Mechanism (b). If the rearrangement of methyl groups is by mechanism (b) or by intermolecular transfer, the calculation must be based on the diluted mevalonolactone used in biosynthesis. Since each sample of 1,422,700 molecules (Exp. I) or 1,001,900 molecules (Exp. II) of the acetic acid contains 10,000 molecules containing $C_{(4)}$ of the undiluted lactone, then each contains 21,500 [Section (3)] molecules containing $C_{(4)}$ of the diluted lactone. Since the ^{13}C content at a labelled position in this lactone is 24·0 + 1·1 = 25·1% [Section (4)], these 21,500 molecules contain 5397 molecules with a ^{13}C-carboxyl group. Now these 21,500 molecules have been supplied with methyl groups from 21,500 other molecules of diluted lactone, including 5397 with a ^{13}C-methyl group. Thus the number of $^{13}C_2$-acetic acid molecules present is $5397 \times (5397/21{,}500) = 1355$, and of $^{13}C_1$-acetic acid molecules $2 \times 5397 \times [(21{,}500 - 5397)/21{,}500] = 8084$. The numbers of molecules of acetic acid from $C_{(2')}$–$C_{(3)}$ of mevalonolactone can be taken as calculated from mechanism (a), since for them dilution before biosynthesis is immaterial. Thus in totals of 21,500 + 29,120 = 50,620 molecules (Exp. I) or 21,500 + 32,100 = 53,600 molecules (Exp. II) of labelled acetic acid there are 1355 + 170 = 1525 molecules of $^{13}C_2$-acetic acid and 8084 + 15,300 = 23,384 molecules of $^{13}C_1$-acetic acid (Exp. I), or 1355 + 187 = 1542 molecules of $^{13}C_2$-acetic acid and 8084 + 16,865 = 24,949 molecules of $^{13}C_1$-acetic acid (Exp. II). Normal abundances for the 50,620 molecules (Exp. I) are 6 molecules of $^{13}C_2$-acetic acid and 1111 molecules of $^{13}C_1$-acetic acid; for the 53,600 molecules (Exp. II), 6 molecules of $^{13}C_2$-acetic acid and 1176 of $^{13}C_1$-acetic acid. Thus the whole sample of 1,422,700 molecules (Exp. I) has 1519 molecules of $^{13}C_2$-acetic acid and 22,273 of $^{13}C_1$-acetic acid above normal; the sample of 1,001,900 molecules (Exp. II) has 1536 molecules of $^{13}C_2$-acetic acid and 23,773 of $^{13}C_1$-acetic acid above normal. Thus the expected proportions by mechanism (b) are

	% excess $^{13}C_1$-acetic acid	% excess $^{13}C_2$-acetic acid
Exp. I	1·57	0·107
Exp. II	2·37	0·153

(8) *Proportions of $^{13}C_2$-acetic acid and $^{13}C_1$-acetic acid, calculated from proportions of mass* 61 *and mass* 62 *found by mass spectrometry*

It has already been deduced (Section (2)) that isotope effects during fragmentation cause $^{13}C_1$-acetic acid to be over-represented to the extent of 2% and $^{13}C_2$-acetic acid to twice this extent. In addition, a correction must be made for the altered distribution of oxygen and hydrogen isotopes in acetic acid containing excess ^{13}C. Most of

this correction is due to ^{18}O. In normal acetic acid, nearly all the 62 peak is formed by $CH_2C^{18}OOH$ ions, but if the acetic acid contains extra ^{13}C some of the ^{18}O is present in molecules of mass 63.

Consider 10^6 molecules of normal acetic acid. These contain 21,954 molecules ($2 \times 0{\cdot}0111 \times 0{\cdot}9889 \times 10^6$) with one ^{12}C atom, 123 ($0{\cdot}0111 \times 0{\cdot}0111 \times 10^6$) with two and 977,923 with none. The oxygen and hydrogen isotopes will be distributed among these three groups. Of the 4000 ^{18}O atoms, 89 are in $^{13}C_1$-acetic acid and 3899 in $^{12}CH_3{}^{12}C^{18}O^{16}OH$. Of the 740 ^{17}O atoms, 16 are in $^{13}C_1$-acetic acid and 723 are in $^{12}CH_3{}^{12}C^{17}O^{16}OH$. Of the 640 D atoms, 14 are in $^{13}C_1$-acetic acid and 621 in $^{12}CH_2D{}^{12}C^{16}O_2H$ or $^{12}CH_3{}^{12}C^{16}O_2D$. Other species are negligible. The number of molecules of mass 60, i.e., $^{12}CH_3{}^{12}C^{16}O_2H$, is

$$977{,}923 - 3899 - 723 - 621 = 972{,}680$$

The number of molecules of mass 61, i.e., $^{13}CH_3{}^{12}C^{16}O_2H + {}^{12}CH_3{}^{13}C^{16}O_2H + {}^{12}CH_3{}^{12}C^{17}O^{16}OH + {}^{12}CH_2D{}^{12}C^{16}O_2H + {}^{12}CH_3{}^{12}C^{16}O_2D$, is

$$21954 + 621 + 723 - 89 - 16 - 14 = 23179.$$

The number of molecules of mass 62, $^{13}CH_3{}^{13}C^{16}O_2H + {}^{12}CH_3{}^{12}C^{18}O^{16}OH + {}^{13}CH_3{}^{12}C^{17}O^{16}OH + {}^{12}CH_3{}^{13}C^{17}O^{16}OH + {}^{12}CH_2D{}^{13}C^{16}O_2H + {}^{13}CH_2D{}^{12}C^{16}O_2H + {}^{12}CH_3{}^{13}C^{16}O_2D + {}^{13}CH_3{}^{12}C^{16}O_2D$, is

$$123 + 3899 + 16 + 14 = 4052.$$

Total 999,911 molecules of mass 60, 61 or 62

$$\% \, 61 = 2{\cdot}318 \qquad \% \, 62 = 0{\cdot}405$$

If the acetic acid contains 1·4% $^{13}C_1$-acetic acid above normal and 0·2% $^{13}C_2$-acetic acid above normal (the approximate figures for Exp. I), there are in 10^6 molecules 35954 molecules of $^{13}C_1$-acetic acid and 2123 of $^{13}C_2$ acetic acid. The numbers of molecules of masses 60, 61 and 62, calculated as above, are

Mass 60 : 956,778
Mass 61 : 37,063 Total 999,849
Mass 62 : 6008

$$\% \, 61 = 3{\cdot}707 \qquad \% \, 62 = 0{\cdot}601.$$

Thus a specimen containing 0·200% excess $^{13}C_2$-acetic acid and 1·40% excess $^{13}C_1$-acetic acid would show in the mass spectrometer 1·39% excess mass 61 and 0·196% excess mass 62, provided that relative peak heights accurately represented relative numbers of molecules. But actually, $^{13}C_1$-acetic acid would be over-represented by 2% and $^{13}C_2$-acetic acid by 4%, so that the observed percentages would be 1·42 and 0·204 respectively. Similarly it can be shown that for a specimen containing 0·300% excess $^{13}C_2$-acetic acid and 2·10% $^{13}C_1$-acetic acid (the approximate figures

for Exp. II) the observed percentage excess for mass 61 would be 2·14 and for mass 62 0·306.

These corrections are now applied to the experimental values for acetic acid from Exp. I and II (Table 8).

TABLE 8. RELATION OF PEAK HEIGHT TO PROPORTION OF ^{13}C SPECIES IN MASS SPECTROMETRY OF ACETIC ACID

Exp.	Observed % excess mass 62	Calculated % excess $^{13}C_2$-acetic acid	Observed % excess mass 61	Calculated % excess $^{13}C_1$-acetic acid
I	0·214	0·210	1·42	1·40
II	0·291	0·285	2·11	2·08

Acknowledgement—Our special thanks are due to Mr. G. Dickinson for the mass-ratio measurements.

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ELECTRONIC SPECTRA OF ORGANIC MOLECULES AND THEIR INTERPRETATION—V*

EFFECT OF TERMINAL GROUPS CONTAINING MULTIPLE BONDS ON THE K-BANDS OF CONJUGATED SYSTEMS

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Abstract—The investigation of the effect of terminal groups of absorbing (conjugated) systems on the corresponding K-bands is extended to groups containing multiple bonds. A consistent theoretical interpretation of all observations is given based on the consideration of the electronic perturbations in the excited state (due to Heisenberg resonance) and the view that organic molecules are built up of localised bonds and involve inductive electron-shifts only. The empirical comparative analysis of the experimental data shows conclusively that, in contrast to the conclusions arrived at by mathematical methods, the 2000 Å, and not the 1800 Å, band system of benzene corresponds to an excited state of the (approximate) symmetry $^1E_{1u}$ (involving an allowed transition characteristic for all K-bands).

INTRODUCTION

AN EARLIER analysis of numerous properties of organic molecules has led to the conclusion that these molecules are built up of localised bonds (orbitals) and that the constitutive charges of these bonds are due to modifications of effective nuclear charges and involve inductive electron displacements only.[1] More recently[2] it has been shown that on this basis a qualitative, but very detailed understanding of all observations related to the electronic spectra of organic molecules becomes possible, if the electronic perturbations in *excited* states (due to wave-mechanical resonance in Heisenberg's original sense) are considered.

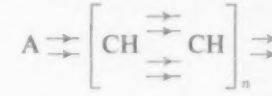
Evidence has been given[3–6] that the electron migration in one direction along an absorbing (conjugated) system (the "effective" electron migration) determines the stability of the excited state corresponding to a K-band. This state can be represented as a "hybrid" of interacting unperturbed excited states each involving one excited electron.

It has been suggested[2] to express this, for convenience, by one simplifying formula only such as (I), in which each arrow corresponds to the excited electron of one unperturbed excited state and also indicates the direction of the electron migration

* Part IV, *Tetrahedron* **4**, 403 (1958).

[1] A. Burawoy, *Contribution to the Study of Molecular Structure* p. 73. Desoer, Liège (1947–48); *Trans. Faraday Soc.* **40**, 537 (1944); *Disc. Faraday Soc.* **10**, 104 (1951); *Chem. & Ind.* **63**, 434 (1944); *J. Chem. Soc.* 3752 (1954).
[2] A. Burawoy, *Tetrahedron* **2**, 122 (1958).
[3] A. Burawoy and E. Spinner, *J. Chem. Soc.* 2085 (1955).
[4] A. Burawoy and E. Spinner, *J. Chem. Soc.* 2557 (1955).
[5] A. Burawoy and A. R. Thompson, *J. Chem. Soc.* 4314 (1956).
[6] A. Burawoy, J. P. Critchley and A. R. Thompson, *Tetrahedron* **4**, 403 (1958).

(on one side of the nodal plane formed) in phase with the effective charge migration of the observed transition. (There is, of course, no intention to attach any importance to the formulation itself.)



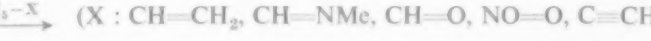
I

A K-band is displaced to longer wavelengths by any structural modification which increases the polarisability of the electrons in the absorbing system, i.e. the stability (of the part-orbitals in phase with the effective electron migration) of the corresponding unperturbed excited states. This may be due either to an *electron-shift* in the ground state coinciding with the direction of the effective charge migration of the transition, which may be caused e.g. by a change of a terminal group or of the solvent, or to a *replacement* of a bond or group (electronic unit) by a more strongly polarisable one.

The discussion of the effect of terminal methyl groups,[3] substituted methyl groups[4] and atoms with lone electron pairs[5,6] of absorbing systems such as (I) on the position of the corresponding K-bands is now extended to the effect of terminal groups containing multiple bonds (I, A or B: CH=CH_2, CH=NMe, CH=O, NO=O, C≡CH, C≡N).

MONOSUBSTITUTED BENZENE DERIVATIVES

Data for the maxima and intensities of the K-bands of benzene, styrene, N-methylbenzaldimide, benzaldehyde, nitrobenzene, phenylacetylene and phenylcyanide in hexane and ethanol solution, as well as the displacements (D) of the benzene K-band (appearing at 2020–2030 Å in various solvents) on introduction of the substituents, are shown in Table 1. The effective electron migration of the transition corresponding to the K-band (observed at longest wavelengths) of these compounds is towards the substituent as indicated by a long arrow in (II).



II

(a) *Styrene, N-methylbenzaldimide, benzaldehyde, nitrobenzene*

The displacements to longer wavelengths of the K-band of benzene in hexane solution (~2020 Å) decrease in the order of substituents CH=CH_2 (D, 430 Å) > CH=NMe (D, 398 Å) > CH=O (D, 388 Å), although the polarity and electron-attracting power of these groups increases in the given order. In these simple compounds, the moderate bathochromic effect to be expected from the electron-shifts in the substituted phenyl group (on introduction of the electron-attracting CH=NMe and CH=O groups) is completely masked by the effect of the electron polarisability increasing in the reversed order —CH=O < —CH=NMe < —CH=CH_2.*

However, in more polar solvents and on substitution of other systems (cf. below) the relative importance of these two factors as well as the order of the polarisability of these groups may undergo appreciable changes. Thus, solvent-solute interactions on replacement of hexane by the more polar ethanol as solvent are responsible (in the ground state) for electron-shifts within the absorbing systems. These shifts are

* Similarly, 1-methylbutadiene absorbs in hexane at longer wavelengths (λ, 2240 Å; ε, 26·000)[7] than crotonaldehyde (λ, 2190 Å; ε, 9300).

[7] K. Bowden, E. A. Braude and E. R. H. Jones, *J. Chem. Soc.* 948 (1946).

negligible in the only slightly polar styrene, appreciable in the more polar N-methylbenzaldimide and highest in benzaldehyde and result in increasing displacements of the K-bands in the given order. Their positions are now almost identical for all three substances (2453, 2450 and 2445 Å respectively).

This effect is even greater on addition of a proton to N-methylbenzaldimide and benzaldehyde respectively, e.g. on salt formation in concentrated sulphuric acid. The increased polarity (and, thus, electron polarisability) of the absorbing system in the ions (III) results in an appreciable displacement of the K-bands to longer wavelengths. The K-band of the conjugate acid of benzaldehyde appears at longer wavelengths (λ, 2950 Å; ε, 26·000) than that of the conjugate acid of N-methylbenzaldimide (λ, 2810 Å; ε, 20·000), because the electron-attracting power and, probably, the electron polarisability of the C=$\overset{+}{O}$H group are greater than those of the C=$\overset{+}{N}$HMe group. (For the greater bathochromic effect of a charged =$\overset{+}{O}$H group as compared with a charged =$\overset{+}{N}H_2$ group in cations and for the significance of this observation, cf. also Burawoy.)[8]

$$C_6H_5{-}CH{=}\overset{+}{O}H \;(=\overset{+}{N}HMe) \qquad \text{III}$$

The K-band of nitrobenzene appears at 2513 Å in hexane and at 2595 Å in ethanol. The effect of the nitro group is similar to that of the formyl group, but the nitro group is more strongly electron-attracting and (mainly for this reason) is responsible for a greater displacement of the benzene K-band (D, 493 Å in hexane and 565 Å in ethanol). In agreement with this interpretation the displacement of the K-band of nitrobenzene on replacing hexane by the more polar ethanol as solvent is greater than that observed for the K-band of benzaldehyde and, indeed, of any other monosubstituted benzene derivative. (For additional spectroscopic evidence, see below.)

(b) *Phenylacetylene, phenylcyanide*

Both the K-bands of phenylacetylene and of phenylcyanide show fine structure which complicates slightly a comparison with the K-bands of derivatives, in which fine structure is absent or less pronounced. The centre of the band systems (2398 and 2245 Å respectively, in hexane) has been chosen for this purpose. Again, there is no relationship between the polarity or electron-attracting power of the C≡CH and C≡N groups and the displacement of the K-band of benzene, the electron polarisability of the more polar C≡N group being considerably smaller than that of the C≡CH group. Moreover, the displacements are also smaller (D, 378 and 225 Å respectively, in hexane) than those caused by the CH=CH_2 and CH=NMe groups (430 and 398 Å respectively). The former groups are more strongly electron-attracting, but possess lower electron polarisabilities.

Replacement of hexane by ethanol as solvent has only a negligible effect (~5 Å) on the position of the K-band system of both phenylacetylene and phenylcyanide, in spite of the appreciable polarity of these molecules. This surprisingly small effect indicates either that the electron-shifts in the ground state of the triple bonds, i.e. their *bond* polarisabilities involving changes of the interatomic distances, or only the electron polarisabilities arising from these electron-shifts are negligible (for discussion, see below).

[8] A. Burawoy, *Ber. Dtsch. Chem. Ges.* **64**, 464, 1635 (1931); **65**, 941 (1932); **66**, 228 (1933); *J. Chem. Soc.* 1177 (1939).

TABLE 1. MAXIMA OF K-BANDS IN Å

X	Solvent	C_6H_5—X →	p-H_2N—C_6H_4—X →	p-O_2N—C_6H_4—X ←
H	EtOH	λ ~2030 ε —	2344[a] 8·000	2595[b] 9·500
	C_6H_{14}	λ ~2020[a] ε 6·600	2340 7·500	2513 9·000
CH=CH_2[b]	EtOH	λ 2453 ε 15·000 D +423 D* —	2770 16·000 +426 +3	3010[c] 14·500 +415 —
	C_6H_{14}	λ 2450[a] ε 14·000 D +430 D* —	2728 19·000 +388 −42	2895 15·500 +382 —
CH=NMe	EtOH	λ 2450 ε 15·000 D +420 D* —	2990 21·000 +646 +226	2800 17·000 +205 —
	C_6H_{14}	λ 2418 ε 15·000 D +398 D* —	2768 23·000 +428 +30	2728 15·000 +215 —
CH=O	EtOH	λ 2445[b] ε 13·500 D +420 D* —	3315 26·500 +971 +551	(2625)[d] — (+30) —
	C_6H_{14}	λ 2408[b,a] ε 14·000 D +388 D* —	2955 22·000 +615 +227	2585[e] 15·000 +72 —
NO=O	EtOH	λ 2595 ε 9·500 D +565 D* —	3725 16·800 +1381 +816	2601[f] 13·000 +6 —
	C_6H_{14}	λ 2513[a] ε 9·000 D +493 D* —	3203 14·000 +863 +370	2556 13·500 +43 —
C≡CH	EtOH	λ 2346, 2444 2395[g] ε 15·000, 13·500 D +365 D* —	2697 20·500 +353 −12	2860 15·000 +265 —

Table 1—*continued*

X	Solvent		C_6H_5—X	*p*-H_2N—C_6H_4—X	*p*-O_2N—C_6H_4—X
	C_6H_{14}	λ	2351, 2446 2398[a,g]	2650	2798
		ε	15·500, 14·500	20·500	16·000
		D	+378	+310	+285
		D*	—	−68	—
C═N	EtOH	λ	2217, 2300 2250[g]	2775	2575[h]
		ε	13·000, 11·000	24·000	14·000
		D	+220	+431	−20
		D*	—	+211	—
	C_6H_{14}	λ	2210, 2296 2245[e,g]	2610	2530
		ε	12·000, 11·000	21·000	13·000
		D	+225	+266	+17
		D*	—	+41	—

D* Increase of displacement by the substituent X as compared with the displacement in the mono-substituted benzene derivative.

[a] For data obtained by Klevens and Platt[11] in heptane solution, see Table 2. [b] Data for styrene and its derivatives are also reported by Pestemer *et al.*[9] [c] Kamlet and Glover[10] give 300 mμ in methanol. [d] Spectrum not obtainable owing to acetal formation. Data extrapolated from those obtained for *p*-nitroacetophenone. [e] Pestemer, *et al.*[9] give 258 mμ. [f] Schubert *et al.*[12] give 260 mμ in 95% ethanol. [g] Estimated centre of band system. [h] Schubert *et al.*[12] give 257 mμ in 95% ethanol.

PARA-SUBSTITUTED ANILINE DERIVATIVES

Data for the maxima of the K-bands of aniline and its derivatives substituted in the *para* position by the CH═CH_2, CH═NMe, CH═O, NO═O, C═CH and C═N groups in hexane and ethanol, the displacements (D) of the maxima on introduction of these substituents, and the differences of the displacements observed in the benzene series and the aniline series (D*) are shown in the second column of Table 1. The effective electron migration is directed, as in the benzene derivatives, towards the substituent as indicated by the long arrow in (IV).

p-H_2N—C_6H_4—X (X: CH═CH_2, CH═NMe, CH═O, NO═O, C═CH, C═N) IV

The displacements (D) of the K-band of aniline (2340 Å in hexane; 2344 Å in ethanol) to longer wavelengths on introduction of the CH═CH_2 and C═CH substituents are slightly smaller, but on introduction of the more polar CH═NMe, CH═O, NO═O and C═N substituents are considerably greater than those observed in the benzene series. The differences in the displacements (D*) increase with the electron-attracting character of the substituents, i.e. in the order CH═CH_2 (−42 Å

[9] M. Pestemer, T. Langer and F. Manchen, *Monatsh. Chem.* **68**, 326 (1936).
[10] M. J. Kamlet and D. J. Glover, *J. Amer. Chem. Soc.* **77**, 5696 (1955).
[11] H. B. Klevens and J. R. Platt, *Technical Report*, Part I. Office of Naval Research (1953–54); *Chem. Rev.* **41**, 301 (1947); *J. Chem. Phys.* **16**, 832 (1948).
[12] W. M. Schubert, J. M. Craven, H. Steadly and J. Robins, *J. Org. Chem.* **22**, 1285 (1957).

in hexane; +3 Å in ethanol) < CH=NMe (+30; +226 Å) < CH=O (+227; +551 Å) < NO=O (+370; +816 Å) and C≡CH (−68; −12 Å) < C≡N (+41; +211 Å). It will also be observed that this effect is considerably greater in ethanol than in the unpolar hexane as solvent.

The band displacements (D) coincide in the aniline series more closely with the polarity of the absorbing molecules. Thus, in hexane solution, the K-bands are displaced to longer wavelengths in the order *p*-aminostyrene (2728 Å) < *p*-amino-N-methylbenzaldimide (2768 Å) < *p*-aminobenzaldehyde (2955 Å) < *p*-nitroaniline (3203 Å) and the differences are even greater for ethanolic solutions (2770, 2990, 3315 and 3725 Å respectively).

Similarly, whereas the K-band of phenylcyanide (2245 Å in hexane; 2250 Å in ethanol) appears at much shorter wavelengths than that of phenylacetylene (2398 and 2395 Å respectively), *p*-aminophenylcyanide absorbs in hexane at only slightly shorter wavelengths (2610 Å) and in ethanol at considerably longer wavelengths (2775 Å) than *p*-aminophenylacetylene (2650 and 2697 Å respectively). Again, whereas the K-band of styrene (2450 Å in hexane and 2453 Å in ethanol) appears at considerably longer wavelengths than that of phenylcyanide (2245 and 2250 Å respectively), the positions of the K-bands of the corresponding aniline derivatives in ethanol are almost identical (2770 and 2775 Å respectively).

These observations are accounted for by the consideration of two factors:

(i) The terminal electron-repelling amino group and the electron-attracting substituents (IV, X) are responsible for (reinforced) electron-shifts within the aniline derivatives, i.e. the polarities of the terminal groups will be considerably greater than those in aniline and in the benzene derivatives C_6H_5—X respectively.* The electron shifts become more pronounced as the electron-attracting power of the substituents (IV, X) increases and as hexane is replaced by the more polar (and possibly hydrogen-bonding) ethanol. They coincide with the direction of the effective charge migration of the transition and, thus, are responsible for increased electron polarisabilities and the resulting displacements of the K-bands to longer wavelengths.

(ii) In absence of any change in the polarity of the substituted absorbing system, the stabilisation of the normal excited state which results from the perturbation (in the excited state) by the electronic system of any substituent, decreases as the length (the number of electrons or possibly the polarisability) of the substituted system increases. This is a generalisation of the well-known fact that the red-shift of a K-band on replacement of a terminal C—H group by the more strongly polarisable C—CH=CH_2 group decreases as the substituted absorbing (conjugated) system is lengthened. For the same reason, this effect is smaller on introduction of a substituent into the *para* position of aniline than into benzene.

This factor will tend to reduce somewhat the discussed bathochromic band displacements to be expected from the increased polarity of the *p*-aniline derivatives and accounts for the negative values of D* observed for the least polar *p*-aminostyrene and *p*-aminophenylacetylene. A more systematic investigation and discussion of this matter will be given in the next communication of this series.

It is noteworthy that the negative value of D* is greater for the K-band of *p*-aminophenylacetylene (−68 Å in hexane; −12 Å in ethanol) than for the K-band of the

* This is generally attributed to increased contributions of polar structures such as $\overset{+}{H_2}N{=}C_6H_4{=}CH{-}O^-$ but are considered by us to involve inductive electron displacements only.

less polar *p*-aminostyrene (−42; +3 Å) and that the values of D* for *p*-aminophenylcyanide (+41; +211 Å) and *p*-amino-N-methylbenzaldimide (+30; +226 Å) are similar, in spite of the great polarity of the former. Moreover, the bathochromic displacement on replacing hexane by ethanol as solvent is of the same order for the K-bands of the former two substances (47 and 42 Å respectively) and considerably smaller for the K-band of the more polar *p*-aminophenylcyanide (165 Å) than for the K-band of *p*-amino-N-methylbenzaldimide (222 Å). These observations again indicate that in triple bonds the electron-shifts in the ground state are either smaller or at least are responsible for smaller increases of their electron polarisabilities (for discussion, see below).

PARA-SUBSTITUTED NITROBENZENE DERIVATIVES

Data for the maxima and intensities of the K-bands of nitrobenzene and its *para*-substituted derivatives in hexane and ethanol, and the displacements (D) on introduction of the substituents into nitrobenzene are, again, enumerated in Table 1. The effective charge migration in all investigated nitrobenzene derivatives is towards the nitro group, i.e. in contrast to the benzene and aniline derivatives the double and triple bonded substituents are now electron-donating terminal groups [see (V)].

$\overleftarrow{p\text{-}O_2N\text{—}C_6H_4\text{—}X}$ (X: CH═CH_2, CH═NMe, CH═O, NO═O, C≡CH, C≡N) V

The displacements (D) to longer wavelengths on introduction of the substituents (V, X) into nitrobenzene are always smaller than those observed in the benzene series and fall rapidly in the order CH═CH_2 (+382 Å in hexane; +415 Å in ethanol) > CH═NMe (+215; +205 Å) > CH═O (+72; +30 Å) > NO═O (+43; +6 Å) and C≡CH (+285; +265 Å) > C≡N (+17; −20 Å). The K-band of *p*-nitrophenylcyanide in ethanol appears even at shorter wavelengths than that of nitrobenzene in this solvent.

In *p*-nitrostyrene, the nitro group is responsible for an electron-shift in the C—CH═CH_2 group which results in an increase of its electron polarisability towards the benzene ring and confers a slightly electron-repelling character to the vinyl group. The greater polarity of *p*-nitrostyrene as compared with nitrobenzene accounts for the slightly larger displacement of the K-band on introduction of the vinyl group in the more polar ethanol (D, +415 Å) than in hexane (D, +382 Å). However, it should be noted that this displacement is in both solvents slightly smaller than that observed for the K-band of styrene (430; 423 Å). As already explained in discussing *p*-aminostyrene, the effect due to the (increased) electron polarisability of the vinyl group in *p*-nitrostyrene is masked by the reduced perturbation effect on substitution of the longer conjugated system of nitrobenzene as compared with that of benzene.

In contrast to the vinyl group, the substituents in all other investigated nitrobenzene derivatives preserve their electron-attracting character. The polarity of these compounds is smaller than that of nitrobenzene itself and, thus, the displacements of the K-bands on introduction of these substituents are smaller in ethanol than in hexane.

The rapid decrease of the band displacements in the order of the electron-attracting power of the substituents is due partly to a decreasing electron polarisability of the substituents towards the *p*-nitrophenyl group and partly to increasing electron-shifts in the substituted O_2N—C_6H_4— system towards the substituent, i.e. in the direction

opposite to that of the effective charge migration of the transition. These contributions cannot be easily separated.

ORIGIN OF THE 2000 Å AND 1800 Å BAND SYSTEMS OF BENZENE

The present investigation completes the discussion of the effect of the more important terminal groups of absorbing (conjugated) systems on the corresponding K-bands. Our analysis confirms earlier conclusions[13] that, quite independent of any detailed theoretical interpretation, the band system of benzene at approximately 2000 Å corresponds to the K-bands of the investigated benzene derivatives and, thus originates in the same allowed transition across the benzene system as indicated by the long arrow in (VI) (A═B═H) (for a more precise interpretation, see reference [2]). This excited state of benzene possesses approximately the symmetry $^1E_{1u}$.

VI

The spectrum of benzene shows, in addition to the K-band system at 2000 Å, a band system of much higher intensity at approximately 1800 Å which according to the invaluable determinations of the vacuum ultra-violet spectra by Price and Walsh[14] and by Klevens and Platt[11] reappears, slightly displaced, in all investigated benzene derivatives. The correspondence of these two band systems of benzene with those observed in the spectra of monosubstituted benzene derivatives is convincingly shown by the data and, even more, by the figures recently published by Klevens and Platt. Some of these data are reproduced in Table 2, together with the displacements (D) on introduction of the various substituents.

TABLE 2. MAXIMA IN Å AND INTENSITIES OF THE K-BANDS AND RYDBERG-BANDS OF SUBSTANCES C_6H_5—X

X	K-band			Rydberg-band		
	λ	ε	D	λ	ε	D
H	2020	6·600	—	1834	46·000	—
Cl	2146	7·500	126	1898	54·000	64
Br	2150	8·000	130	1908	36·000	74
I	2278	11·500[5]	258	1946	90·000	112
CH═CH_2	2463	15·000	443	2033	23·000	199
CH═O	2404	15·000	384	2004	26·000	170
C≡CH	2386	16·000	366	1992	30·000	158
C≡N	2223	17·000	203	1880	44·000	46
NO═O	2513	8·000	493	2062	13·000	228
HO	2128	6·000	108	1898	50·000	64
H_2N	2353	8·000	333	1968	32·000	134

The 1800 Å band system of benzene and, thus, the corresponding bands of the benzene derivatives should be assigned to Rydberg transitions originating in the double bonds of benzene.[13] This interpretation is in agreement with the high intensities

[13] A. Burawoy, *Disc. Faraday Soc.* **9**, 73 (1950).
[11] W. C. Price and A. D. Walsh, *Proc. Roy. Soc.* A **191**, 22, 32 (1947).

of these bands. It also accounts for the much smaller band displacements observed on introduction of substituents, since the symmetry characteristic for a Rydberg transition which is probably localised in only one of the double bonds of benzene (nodal plane in the bond axis) is different from the symmetry of the "unperturbed" states involving the excited electrons of the substituents (nodal plane perpendicular to the bond axis). This should result in a smaller degree of interaction.

Attempts to account for the excited states of benzene by the application of mathematical methods have led to the conclusion that the 2000 Å band system, in spite of its rather high intensity (ε, 6000–7000), corresponds to a forbidden transition ($^1B_{1u}$ or $^1E_{2u}$) and that it is the band system at 1800 Å which may correspond to an excited state of symmetry $^1E_{1u}$ (characteristic for K-bands).

Kauzmann[15] has summarised the conclusions of a very detailed and critical analysis of these methods to which reference should be made: "The theoretical account of the spectrum of benzene is therefore only partially satisfactory. There seems to be little doubt that the lowest excited singlet state is of the $^1B_{2u}$-type, that a triplet state should lie somewhere below it, and that there is a $^1E_{1u}$-level at some distance above it. Other details of the energy level diagram are, however, still not at all clear, and it is doubtful if calculations capable of resolving these uncertainties are feasible at the present time." Obviously, the results of mathematical calculations cannot be taken to represent evidence for the correct assignment of the 2000 Å and 1800 Å band system of the benzene spectrum.

It is, therefore, most significant that the assignments of the band systems arrived at by the mathematical methods are already *qualitatively* in disagreement with the available experimental observations, the empirical comparative analysis of which allows no doubt that the excited state of symmetry type $^1E_{1u}$ corresponds to the 2000 Å band system and not to the 1800 Å band system, and that the latter involves electronic transitions of the Rydberg type.

This lends strong support to the view[1] that, apart from the limitations and inadequacies of the mathematical methods discussed by Kauzmann, the simplifying qualitative structural assumptions such as the consideration of the π-electrons only and their "vertical"* arrangement in non-localised orbitals—which form the common basis of all approximations hitherto applied to the interpretation of more complicated structures such as benzene—are also at fault. These assumptions only *appear* to be justified because electronic repulsions (and related polarisation effects) are insufficiently considered.

GENERAL DISCUSSION

The theoretical interpretation of electronic spectra of organic molecules and, in particular, of the effect of terminal groups of absorbing (conjugated) systems on the position of K-bands advanced in the preceding papers of this series accounts consistently for the observations reported in the present communication.

The wave-mechanical resonance characteristic for the electronic perturbations in the excited states of polyelectronic systems represents a physical phenomenon which is absent in the ground state.[2] Thus, the introduction of a substituent possessing an electron affinity similar to the hydrogen atom, e.g. the vinyl group in styrene, will be

* The π-electrons are assumed to be moving within orbitals in the common potential field of the nuclear frame-work of benzene including the σ-electrons, similar to the valency electrons in an atom.

[15] W. Kauzmann, *Quantum Chemistry* pp. 375–478. Academic Press, New York (1957).

responsible in the *ground state* for only a *negligible* change in the electron system of the substituted phenyl group, but displaces the K-band *strongly* to longer wavelengths as a result of the increased perturbation by the electron system of the substituent in the *excited state*.

On the other hand, factors (solvents, substituents, proton addition) responsible for electron-shifts in the ground state of an absorbing system which coincide with the direction of the effective charge migration make an additional contribution to the stability of the normal excited state, i.e. they displace the corresponding K-band to longer wavelengths.

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There is, however, no simple relationship between the polarity and the electron polarisability of *different* groups or systems. This has already been shown for all terminal groups C—X,[5,6] in which X is an atom with unshared electrons. The electron polarisability increases both in benzene derivatives C_6H_5—X and in the *p*-aniline derivatives H_2N—C_6H_4—X approximately in the same order of groups C—F < C—H < C—OH < C—Cl < C—Br < C—I < C—NH_2 < C—SH. This order is not related to the polarity of the covalent bonds and, what is more important, is approximately the same, whether these groups are at the electron-donating or the electron-receiving end of the charge migration of the transition.* This is accounted for by the fact that these groups are treated as units and that the polarisability of the bonding electrons is completely masked by the contribution of the increasing polarisability of the unshared electrons in the observed order (the effect of which is mainly transmitted through the covalent bond).

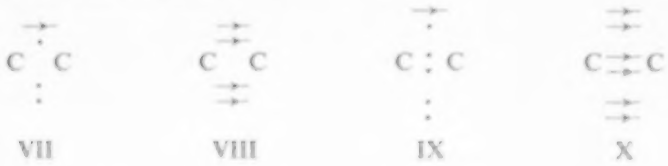
Similarly, the electron polarisabilities of the CH═O group and of the C≡N group in benzaldehyde and phenylcyanide are smaller than those of the CH═CH_2 group and of the C≡CH group in styrene and phenylacetylene respectively, although qualitatively the reduced ionisation potential of the carbon atoms and the increased electron affinity of the participating atom in the more polar bonds could have been expected to be responsible for greater electron polarisabilities.

These observations can be accounted for by assuming that the polarisabilities of the unshared electrons attached to double or triple bonded oxygen and nitrogen atoms are smaller than those of the corresponding bonding C—H electrons. The high effective nuclear charge at atoms participating in double and triple bonds is known to be responsible for shorter and stronger bonds with all substituents including the hydrogen atom. The increase of the binding energies of the non-bonding electrons can be expected to be even greater, since their attraction is not hindered by nuclear repulsions (for discussion of this matter and literature, see reference[1]). In agreement with this interpretation, the difference in the electron polarisabilities of the triple bonded C≡CH and C≡N groups (D, 378 and 225 Å, respectively) is much greater than the difference observed for the corresponding double bonded CH═CH_2 and CH═NMe groups (D, 430 and 398 Å, respectively).

The smaller polarisability of the non-bonding electrons or of the bonding C—H electrons in triple bond groups should also partly account for the observation that the total electron polarisability of these groups is smaller than that of double bond groups, but, in this case, an additional factor should be taken into consideration. As recently[2] pointed out, the excited state of a double bond can be described as a resonance

* It should be noted, however, that the electron polarisability of these groups is always considerably greater towards the aromatic carbon atom than in the opposite direction.

hybrid of four equivalent unperturbed excited states each involving one excited electron as indicated in the abbreviating formula (VIII). Its stability will be a function (i) of the stability of each unperturbed excited state (VII) and (ii) of the destabilisation arising from their mutual interactions.



VII VIII IX X

Similarly, the stability of the excited state of a triple bond (X) will be a function of (i) the stability of each unperturbed excited state (IX) and (ii) of the destabilisation arising from the interaction of six such states. Although it is probable that each unperturbed excited state of a triple bond will be more stable (i.e. will involve a smaller transition energy) than that of a double bond, the *destabilisation* should be greater for the triple bond, since it arises from the interaction of the greater number of such states. A mathematical analysis of this matter should be of great interest.

This interpretation also accounts for the observed surprisingly small effect of solvents and polar substituents on the electron polarisability of triple bonds (see above). This cannot be attributed to a negligible transmission of polar effects along triple bonds, since it has been recently[16*] shown that the introduction of an alkyl group into the 3-position of both 1:1-dimethylprop-2-ynyl chloride $HC{\equiv}C{-}CMe_2Cl$ and allyl chloride[17] $H_2C{=}CH{-}CH_2Cl$ has a very appreciable and similar (1000-fold) effect on their rates of ionisation.

However, assuming an equal *total* electron-shift, the shift of each *individual* electron will be smaller in a triple than a double bond. This will result in a smaller increase of the stability of each unperturbed excited state and, thus, of the electron polarisability of the triple bond which effect will be further enhanced by the greater degree of destabilisation arising from the increased interaction of six rather than four unperturbed excited states.

EXPERIMENTAL

The spectral determinations were generally carried out with a Hilger E3 quartz spectrograph fitted with a Spekker photometer, a tungsten-steel high tension spark being employed as the source of light. The spectra of phenylacetylene, phenylcyanide and *p*-aminobenzaldehyde were measured with a Hilger Uvispek Photoelectric Spectrophotometer. All investigated substances were obtained in a high state of purity. *p*-Nitro-N-methylbenzaldimide, *p*-amino-N-methylbenzaldimide and *p*-aminoacetylene have not been previously described.

p-*Nitro*-N-*methylbenzaldimide*. *p*-Nitrobenzaldehyde (15·8 g) and aqueous methylamine (100 cc of a 33% w/v solution) were heated on a water-bath for 30 min. On cooling, the initially formed oil solidified. Yield: 15 g; 85% of theory. *p*-Nitro-N-methylbenzaldimide crystallised from ethanol as small yellow plates of m.p. 106°. (Found: C, 58·8; H, 5·0; N, 17·0; Calc. for $C_8H_8N_2O_2$: C, 58·5; H, 4·9; N, 16·4%).

* The rate of hydrolysis of allyl chloride [given as 10^6k_1 (sec^{-1})] reproduced in Table 1 of this paper should be 0·00036 and not, as printed, 0·000036.

[16] A. Burawoy and E. Spinner, *J. Chem. Soc.* 3752 (1954).
[17] C. A. Vernon, *J. Chem. Soc.* 423 (1954).

p-*Amino*-N-*methylbenzaldimide*. A solution of *p*-aminobenzaldehyde (10·0 g) in an excess of aqueous methylamine (33% w/v) was allowed to stand for 20 hr. The solvent was evaporated over potassium hydroxide in vacuo. The residue consisting of almost pure *p*-amino-N-methylbenzaldimide crystallised from aqueous methylamine as colourless needles of m.p. 90–91°. Yield: 9·0 g, 80% of theory. Exposed to air, the crystals soon turned yellow (probably due to salt formation with carbonic acid). (Found: C, 71·4; H, 7·6; Calc. for $C_8H_{10}N_2$: C, 71·6; N, 7·4%).

p-*Aminophenylacetylene*. *p*-Nitrophenylacetylene[18] (10 g) was shaken for 24 hr with zinc dust (3·0 g), ammonia (4 cc, 0·88 sp. g.), and water (3 cc) at room temp., water-cooling being applied at the onset of the reaction. The mixture was steam-distilled and the distillate extracted with ether. After removal of ether, the residue of almost pure *p*-aminophenylacetylene was collected. Yield: 0·72 g, 90% of theory. Crystallisation from light petroleum (b.p. 60–80°) gave colourless needles of m.p. 100°. (Found: C, 82·4; H, 5·8; N, 12·0; Calc. for C_8H_7N: C, 82·1; H, 5·9; N, 12·0%).

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NOTE

Secondary hydrogen isotope effects and vibrational frequency shifts

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We have recently reported that trideuteration in the methyl group of toluene, or in one such group of *m*-xylene, reduces the equilibrium constant of π-complex formation with chloranil by about 7 per cent.[1] This effect is in the same direction as those found in solvolysis, where hyperconjugative electron release from a β- or *para*-CD_3 group is interpreted as being less effective than from a CH_3 group.[2,3] Streitwieser and his collaborators[4] have recently amplified and rendered quantitative the usual view that these effects arise from the crowding of vibrational levels in the electron deficient transition state (or product molecule in an analogous thermodynamic effect). In their model, since the toluene moiety of the complex is certainly electron deficient relative to toluene itself, the observed effect is in the predicted direction, its magnitude requiring a total shift to lower frequencies of some 100 cm^{-1}, shared amongst the six methyl stretching and bending modes.

We have noted that the isotope effect for one CD_3 group is the same in toluene and *m*-xylene. The standard free energy of complex formation varies in a roughly linear manner with the number of methyl groups,[5] so that each methyl group can be considered as acting independently. Furthermore, the methyl frequencies of different polymethylbenzenes are nearly identical.[6,7] It follows that the "level crowding" hypothesis can be tested by a comparison of the infra-red spectra of hexamethyl-

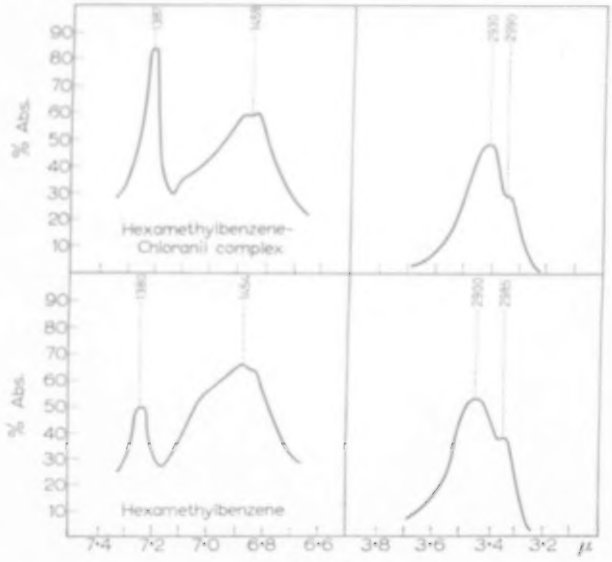

FIG. 1.

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[3] V. J. Shiner, Jr. *J. Amer. Chem. Soc.* **75**, 2925 (1953); and subsequent papers.
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[5] R. Foster, D. Ll. Hammick and B. N. Parsons, *J. Chem. Soc.* 555 (1956).
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benzene with that of its solid complex with chloranil[8] (both in KBr). In the two relevant regions chloranil is transparent and hexamethylbenzene has no other infra-red active fundamentals.[9]

It is clear from Fig. 1 that the relevant bands shift to *higher* frequencies in the complex, the total shift estimated for the six methyl modes being about 50 cm^{-1}. Evidently in this system, and perhaps in general, hyperconjugative electron release from a methyl group does not lower the appropriate force constants, and the observed isotope effect, which is almost certainly related to hyperconjugative electron release, occurs *in spite of* frequency shifts and not because of them.

Streitwieser *et al.*[4] have also interpreted the effect of deuteration on acid and base strength[10] in terms of vibrational frequency shifts. The frequencies from recent vibrational analyses of acetate ion[11] and acetic acid,[12] introduced in their equations,[4] do not account for an appreciable isotope effect in either direction.

It is clearly advisable to refrain from applying the "level crowding" hypothesis to any and all isotope effects until convincing experimental evidence in its favour is obtained. No such objection, however, applies to Streitwieser's "α-effect",[4] where a definite hybridisation change occurs.

The necessity of considering both inductive and hyperconjugative effects has been pointed out in an earlier communication.[13] On the basis of recent theoretical work[14] we believe that *both* types of effect can be ascribed to configurational differences arising from the anharmonicity of the symmetrical stretching and bending modes.[15]

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